The Journal
OF THE KANSAS MEDICAL SOCIETY

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References
(1) Kirby, W. M. M.; Waddington, W. S., & Doornink, G. M.: Antibiotics Annual, 1953-1954, New York, Medical Encyclopedia, Inc., 1953, p. 285.
(2) Finland, M., & Haight, T. H.: *Arch. Int. Med.* **91**:143, 1953.

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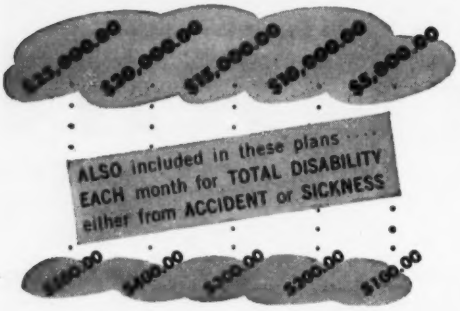

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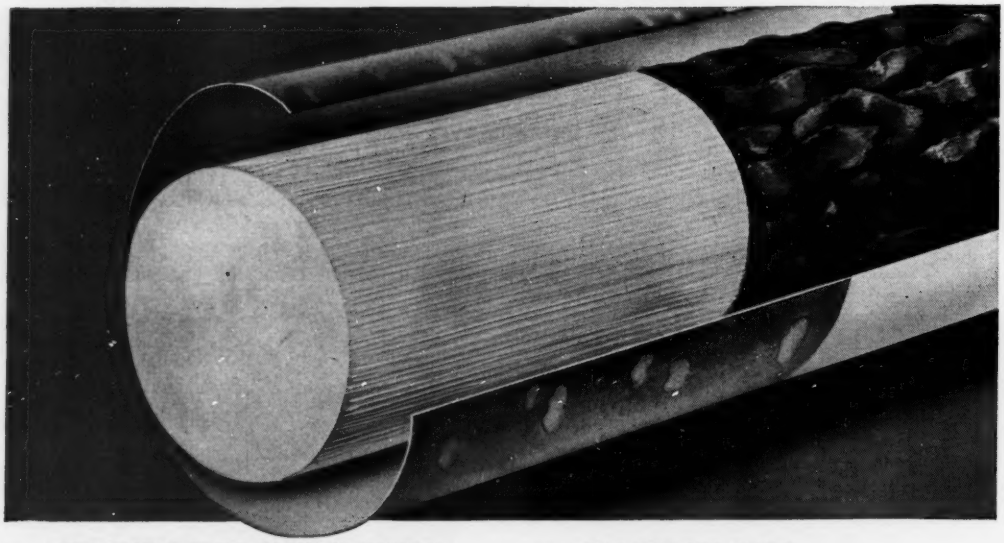

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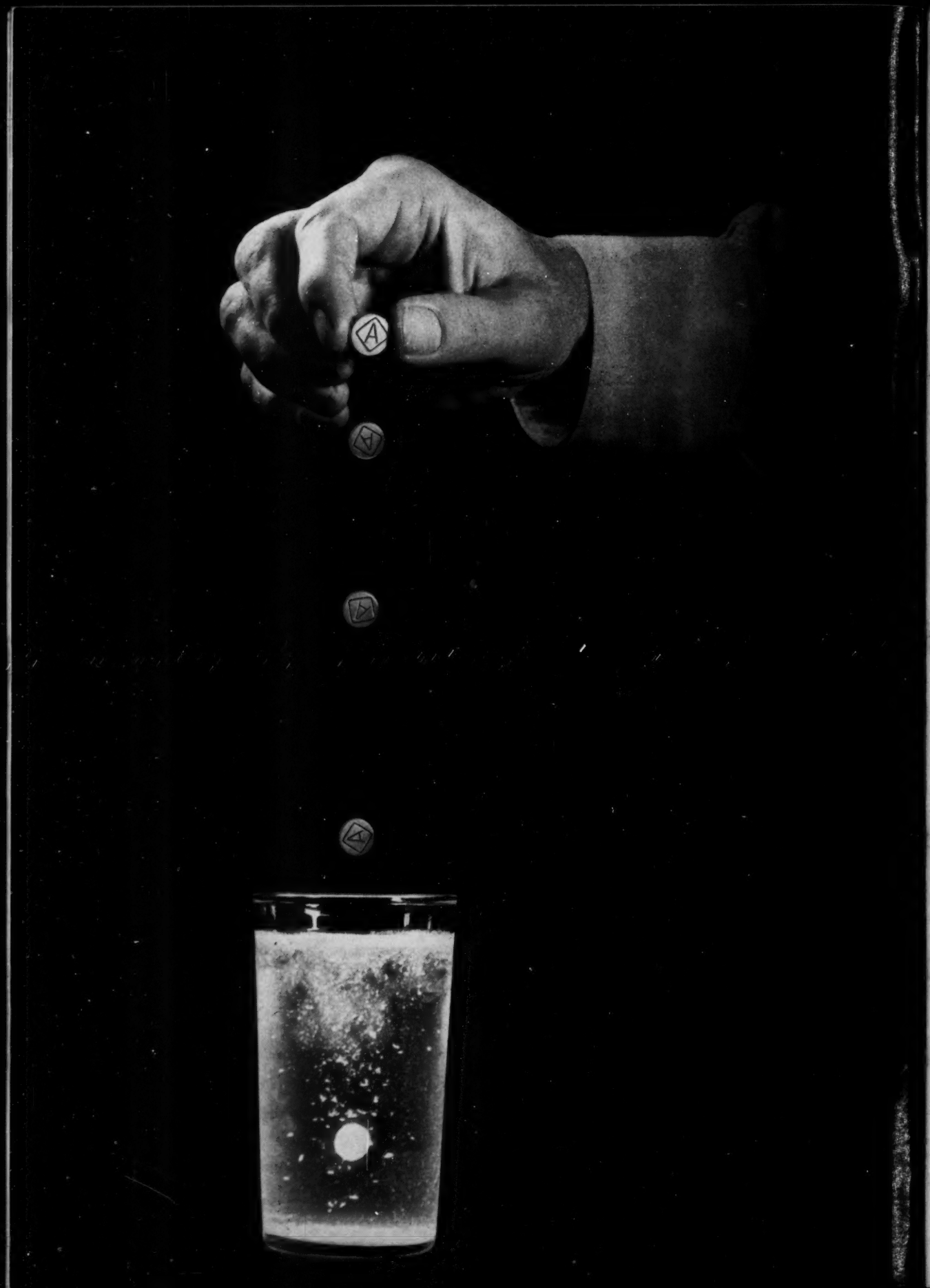

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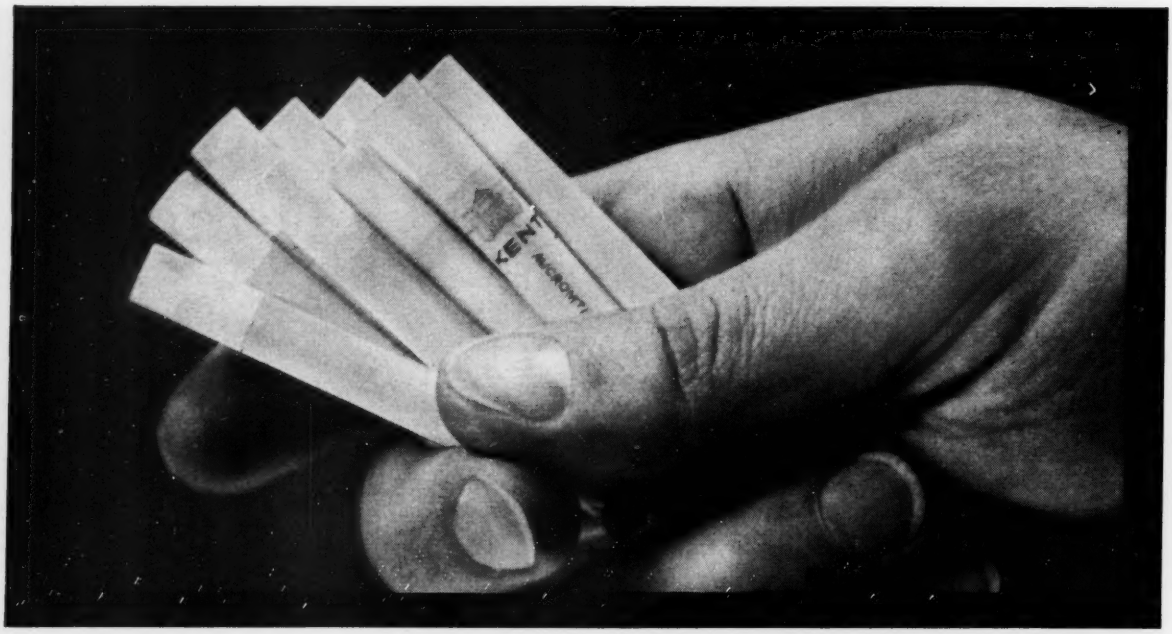

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1. Malleson, J.: Lancet 2:158 (July 25) 1953. 2. Goldzieher, M. A., and Goldzieher, J. W.: Endocrine Treatment in General Practice, New York, Springer Publishing Company, Inc. 1953, p. 23.

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Volume LV SEPTEMBER, 1954 No. 9

Lung Cysts

Melvin A. Rabe, M.D.*
Leavenworth, Kansas

Lung cysts are neither a new nor rare disease, but awareness of and interest in this disease entity has been comparatively recent. For the most part it has paralleled the development of thoracic surgery.

HISTORICAL BACKGROUND

Koontz[1] in 1925 reviewed the World's literature on cystic disease of the lung and found a total of 108 cases including allied conditions such as tracheal diverticula, cysts of aberrant lung tissue, etc. Most of these cases were reported by the Germans and at autopsy. There were *no* reports in the American literature at that time.

Eloesser[2] in 1931 could find but four reports of cystic disease of the lung in the American literature and added four cases of his own.

Wood[3] in 1934 reviewed twenty-three cases from the literature and added sixteen of his own. Interestingly, the treatment at that time seemed to be in doubt with only a few cases subjected to definitive surgical therapy.

Schenck[4] in 1937 stated that a total of only 381 cases of cystic disease of the lungs had been reported since the original description. This was several years after some of the monumental strides in chest surgery had already been made. The first successful pneumonectomy by Nissen[5] had been done and successful pneumonectomy for carcinoma had been carried out by Graham,[6] both in 1933. The modern technic of individual ligation of hilar structures had been developed by Rienhoff[7] later that same year, but thoracic surgery did not attain wide application for several years thereafter. The introduction of the technic of segmental resection by Churchill and Belsey[8] in 1939, together with increasing knowledge of thoracic physiology and anesthetic technics, set the stage for the surge of interest in chest surgery in World War II. Increasing awareness of chest diseases amenable to surgery, including cystic disease of the lung, is apparent in the literature from that time to the present. Indeed it has only been since World War II that reports of numerous cases of lung cysts have become fairly common in the literature.

PATHOLOGY

The nomenclature and pathogenesis of lung cysts still seems to be confused and controversial. Cooke and Blades[9] divide them into two types: congenital and acquired, considering only bullous emphysema and subpleural blebs as acquired lesions and dividing the congenital cysts into bronchiogenic and alveolar types.

Maier and Haight[10] classify them into two groups according to the presence or absence of an epithelial lining. They state that the epithelialized group may be congenital or acquired. The wall of a congenital epithelialized cyst may contain bronchial elements such as cartilage, glands, and smooth muscle. The acquired epithelialized cyst usually does not have cartilage and muscle in the wall; epithelialization results from an ingrowth of epithelium from the bronchial fistulas in the same manner as in an epithelialized, chronic, pulmonary abscess. The nonepithelial-

* Attending Surgeon, Veterans Administration Center, Wadsworth, Kansas.

One of the case reports in this article is from the Veterans Administration Center, Wadsworth, Kansas. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

ized pulmonary cyst has a wall consisting merely of thin connective tissue without epithelium. There may be some flattened connective tissue cells in areas presenting a mesothelial lining, but there are no bronchial elements in the wall. Compressed alveoli surround the thin connective tissue lining. There is no definite line of distinction between these pulmonary cysts or pneumatoceles and bullous emphysema.

Moersch and Clagett[11] divide all pulmonary cysts into two chief types: those that originate from the bronchial tree and those that are alveolar in origin. Bronchiogenic cysts are characterized by the fact that they possess an epithelial lining which may or may not be ciliated. In contrast those cysts which are alveolar in type do not possess an epithelial lining but are lined with alveolar cells that are compressed together to form the wall.

There is also a variance of opinion regarding the etiology of these lesions. Practically all of the early writers seem to take for granted that these lesions were congenital. In contrast most of the present day workers, with the notable exception of Blades and his associates, seem to feel that many if not most of these lesions are acquired. This was first pointed out by Peirce and Dirkse[12] in 1937 who stated: "The common lack of information in regard to the antecedent respiratory history of patients with cystic pulmonary disease raises grave doubt of the propriety of the term 'congenital' in a roentgenologic diagnosis of cystic disease." They report a series of cases tending to substantiate a diagnosis of acquired cystic disease and quote Dr. Carl J. Weller, Director of the University of Michigan Pathology Laboratory, as stating that he has never seen changes in the lungs of infants or young children which would permit the diagnosis of congenital cystic disease of the lung. They conclude that a congenital origin for cystic pulmonary disease is doubted as a valid premise in a majority of cases. Ackerman[13] states that congenital cystic disease is often incorrectly diagnosed and the criteria for its recognition are poorly defined. He points out that lung abscesses may heal leaving a large unilateral cyst with a smooth lining and that alveolar cysts may form by the rupture of an alveolus into adjoining alveoli with the formation of a large air space by compression of the residual nondiseased lung as it enlarges. Thus both the so-called alveolar and bronchiogenic cysts may be acquired.

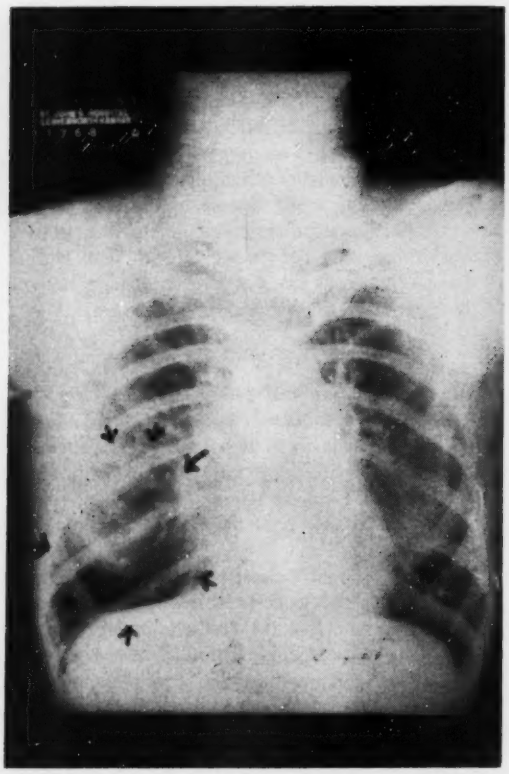

Fig. 1 (S. M.) 29 year old white female. Original film 2-47-51 in which a lung cyst at the base of the right lung was discovered. It is barely visible in the picture and is marked by arrows. It is more apparent on the film but could easily be missed by casual inspection.

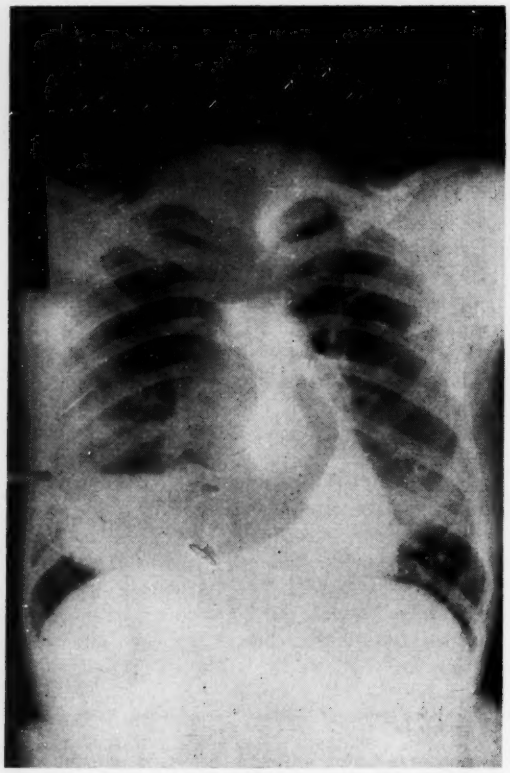

Fig. 2 (S. M.) Same patient 2 years later showing collection of fluid in cyst.

DIAGNOSIS AND TREATMENT

Moersch and Clagett in a review of 44 cases state that the symptomatology of the disease is dependent upon the status of the bronchial communication and the presence or absence of infection. In their series, cough, expectoration, hemoptysis, dyspnea, and pain were the most prevalent symptoms and in that order of frequency. Many cases are of course asymptomatic, especially those that are uninfected and those that have no bronchial communication. The incidence of relatively asymptomatic lung cysts is seen in a mass chest survey taken at Ft. Leavenworth, Kansas,[14] where four cases of lung cysts were found in a series of 3,435 routine chest x-rays of the population of the Post. The diagnosis is best made by means of chest x-rays which should include a lateral projection. Bronchography may occasionally be helpful, especially to differentiate cystic bronchiectasis. Bronchoscopy rarely gives much diagnostic aid.

The disease must be differentiated from pulmonary tuberculosis, pulmonary abscess, carcinoma, mediastinal tumors, empyema and pneumothorax. Fluid filled cysts have been mistakenly treated as empyema, and giant air cysts have been treated as spontaneous pneumothorax and subjected to aspiration of air.[15] When the diagnosis is in doubt, exploratory thoracotomy is advised by most authorities.

The treatment of the disease is entirely surgical and should be carried out even though the lesion is asymptomatic. This is to avoid the possibility of allowing more serious lesions to remain because the diagnosis cannot be positively made, as well as to prevent the development of carcinoma in the cyst, which was found in over 5 per cent of the cases reported by Moersch and Clagett. Then too, the asymptomatic cysts are prone to become symptomatic with the passage of time, especially if they have a bronchial communication. The surgical procedure advised by Dickson et al[16] is one which will extirpate the cyst with conservation of as much functioning lung as possible. This may be done by enucleation or wedge resection although occasionally lobectomy or rarely even pneumonectomy may be necessary. Allbritten and Templeton[17] recommend that single large cysts of the lung be treated by simple excision of the walls of the space, closure of bronchiolar fistulas, and obliteration of the pleural space by re-expansion of the lung with catheter drainage and suction.

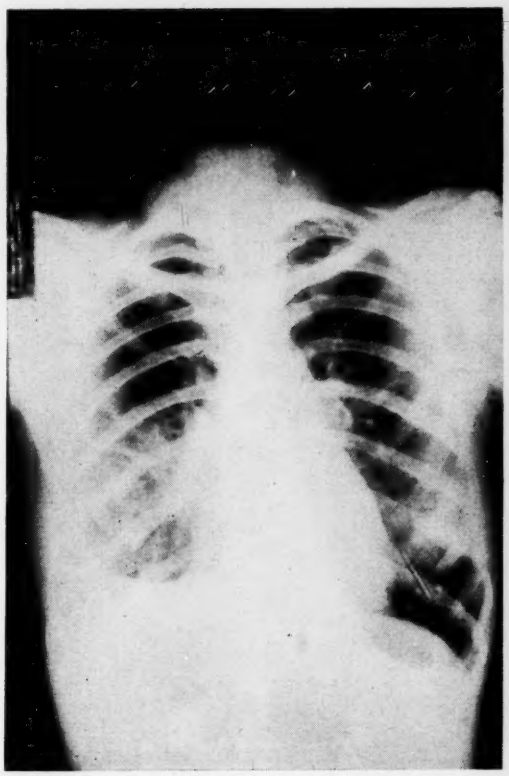

Fig. 3 (S. M.) Same patient postoperatively.

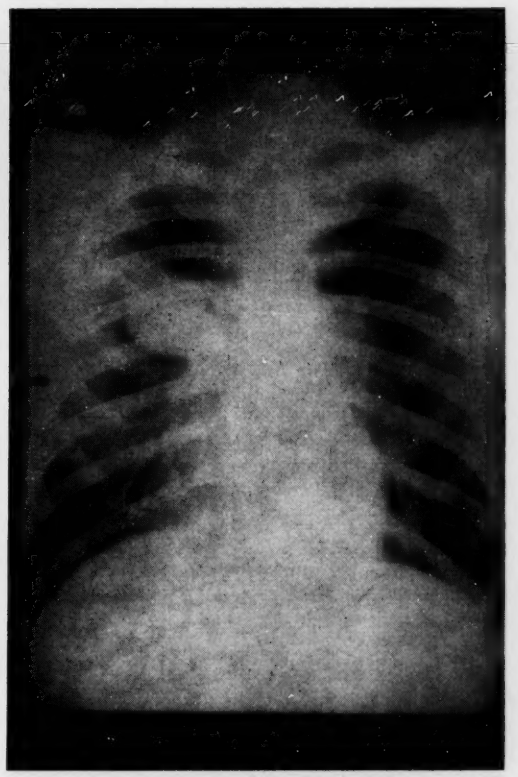

Fig. 4 (D. D.) 32 year old white male showing radio-opacity in right upper chest which proved to be a pulmonary cyst.

CASE REPORTS*

Case No. 1 (S. M.)

This white female was 29 years old when the original chest film made on 2-17-51 showed a cyst at the base of the right lung. She had a history of cough and expectoration each winter since a severe case of pneumonia at age of 15. The original x-ray film showed a very slight amount of fluid in the cyst and no particular reaction around it (Fig. 1). It was decided to treat the patient conservatively at that time. Subsequent films showed a fluid level in the cyst and an increase in the thickness of the wall probably due to pneumonitis, and surgical removal was decided upon (Fig. 2).

Thoracotomy was done on 4-27-53, some two years after the cyst was originally discovered. The cyst was adherent to the posterior chest wall, lying very superficially in the lower lobe and was opened and dissected out, much like a hernial sac. Several small bronchial communications were closed. The patient's convalescence was essentially uneventful and follow-up several months later showed almost complete elimination of cough and expectoration. The post-operative x-ray is shown in Fig. 3.

PATHOLOGICAL REPORT

Specimen consists of a cyst which has been collapsed and in the collapsed state measures 5.5 x 4 x 2.5 cm. The outer surface is brown and in some areas is irregular and roughened while in other portions it is smooth. The cyst lining measures 1 to 2 mm. in thickness with a smooth inner surface. The wall measures 1 mm. in thickness in some areas while in other areas compressed atelectatic lung tissue is present measuring up to 8 mm. in thickness. Histological sections are those of lung in which a cyst is present in the central portion in which the overlying epithelium is absent in most areas but can be identified as being tall columnar respiratory epithelium in others. The wall of the cyst is composed of dense collagenous fibrous tissue in which remnants of bronchi and lung parenchyma are seen. More peripherally there is more compressed atelectatic lung tissue in which dilated bronchi are noted lined with columnar epithelium.

Diagnosis: Cyst of the lung with surrounding compression atelectasis and bronchiectasis. The pathol-

* Two of these three cases were first seen and diagnosed by Dr. G. S. Voorhees, Leavenworth, Kansas.

Fig. 5 (D. D.) Same patient after a right upper lobectomy.

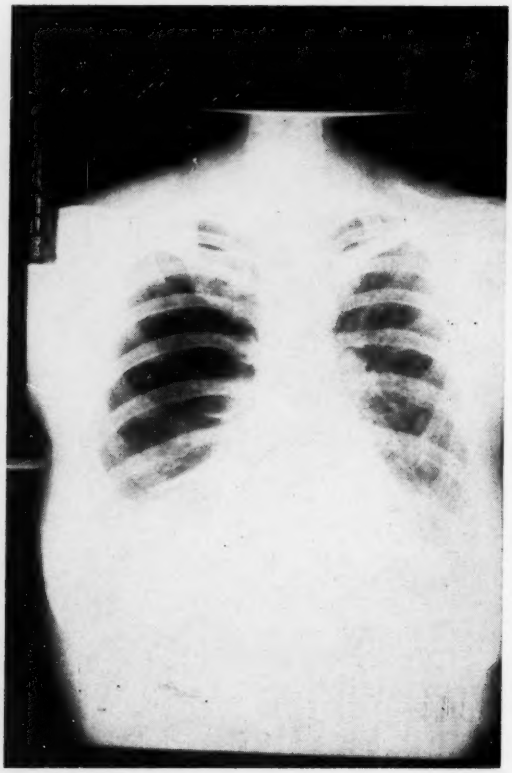

Fig. 6 (B. L.) 42 year old white female showing almost complete absence of right upper lung fields.

ogist makes the comment that "the etiology of this cyst cannot be determined by microscopic section. The histological pattern would fit the diagnosis of a congenital cyst although an acquired cyst cannot be excluded."

Case No. 2 (D. D.)

This 32 year old white male was admitted to the Veterans Administration Hospital, Wadsworth, Kansas, on 9-28-53. One month previously a mass chest survey in his town by the State Public Health Service revealed a lesion in his chest, and hospitalization was advised by his local physician. He had been completely asymptomatic previously, although three years before a routine chest x-ray also apparently revealed a lesion, for the patient was advised at that time to consult his local doctor. The only significant past history was one attack of pneumonia at age 19. Tuberculin, coccidiodin, and histoplasmin skin tests were negative. Bronchoscopy was negative.

The x-rays (Fig. 4) were reported as follows: "The right lung field shows a homogenous lobulated density measuring approximately 8 cm. in its greatest diameter and extending into the lung parenchyma from the right hilar area which appears to lie on the lateral film at approximately the junction of the anterior and middle mediastinum. The possibilities here could be those of a pulmonary aneurysm or an arteriovenous fistula. One must also consider a neurofibroma, dermoid cyst, hamartoma or lymphosarcoma."

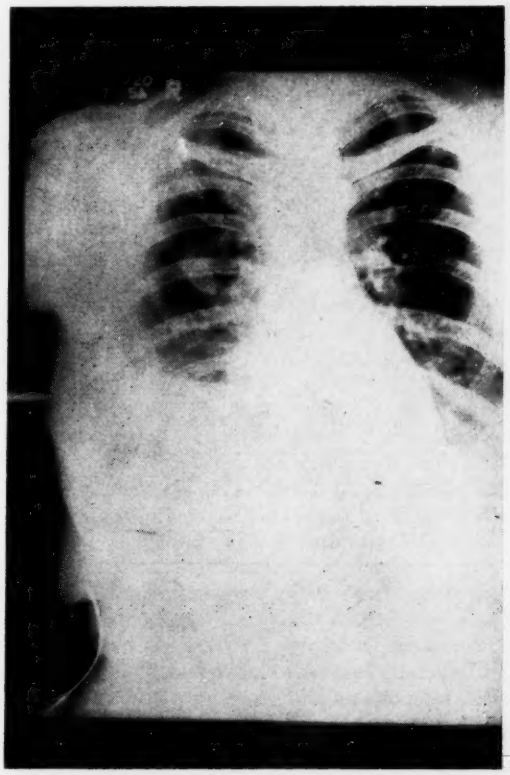

Fig. 7 (B. L.) Same patient postoperatively after extirpation of huge air-filled cyst. The right upper lung field markings are now apparent.

At operation, a cystic structure attached to, but not communicating with the right upper lobe main bronchus, was found and upper lobectomy was performed. The cyst contained viscous and grumous material. Postoperative course was uneventful except for an atelectasis which was relieved by bronchoscopy. The postoperative x-ray is shown in Fig. 5.

PATHOLOGICAL REPORT

The specimen consists of tissue labeled right upper lobe of lung. On palpation one can feel a rather firm mass within the depth of the lobe. On section this is shown to be a multiloculated, cystic cavity which measures approximately 6 cm. in its greatest diameter. The cavity is lined with a thickened, fibrous appearing yellowish gray membrane which is roughened in many areas. Multiple dissections into smaller bronchi in the area and the lobe reveal no definite gross connections between bronchi or bronchioles and the loculated cyst.

Histological sections show a thick walled cystic space that is lined in some areas with intact remnants of respiratory epithelium. Throughout much of the section, however, the epithelial lining is absent, and the surface is covered with pseudo-granulation-like-tissue containing large numbers of lipid laden macrophages. The wall is quite thick, fibrous, and shows infiltration with lipid laden macrophages and mononuclear leukocytes. Smaller bronchioles in the cyst wall show considerable dilatation and are surrounded with cuffs of lymphocytes. On the basis of histology alone, a diagnosis of bronchiectasis was entertained.

Case No. 3 (B. L.)

This 43 year old white female had a large air-filled cyst discovered on a routine chest survey. After the lesion had been found, interrogation of the patient revealed that she had noticed progressive dyspnea on exertion for a period of six months. She was a trained, though not professional, singer and required considerable vital capacity which she noticed to be somewhat reduced during this period. This is understandable on viewing the x-ray film which shows obliteration of the right upper lung fields. (Fig. 6)

Thoracotomy done on 12-9-53 revealed a large air-filled cyst arising from the anterior portion of the upper lobe. It was adherent to the visceral pleura in several areas and its attachment to the upper lobe was almost like a pedicle. It was excised and a few small communicating bronchioles closed. There was

a small emphysematous bleb nearby which was also excised. The patient's convalescence was uneventful. The postoperative x-ray is shown in Fig. 7.

PATHOLOGICAL REPORT

Material consists of a distorted mass of lung tissue measuring 5 cm. in diameter. This ball can be unfolded revealing a flattened sheet of tissue 15 cm. in length with thin walls of fairly uniform thickness. There are some trabeculations on one side of the wall. There is a small amount of lung tissue, and its pleural surface is smooth and glistening and shows some anthracotic pigmentation. Histological sections through the lung show extensive atelectasis and replacement fibrosis. The cyst wall is made of dense fibrous tissue with lymphocytes imbedded in it. The wall is undergoing collagenous degeneration of marked degree, and the lining has largely been denuded.

Diagnosis: Large fibrous walled cyst of the lung with surrounding atelectasis.

COMMENT

These three cases of lung cysts, seen within a period of a year in a general surgical practice, are a suggestion of the increasing frequency with which this disease is being recognized, for it was unknown in American literature less than thirty years ago. These cases are also interesting because they represent three different kinds of cysts.

Case No. 1 is a typical bronchiogenic cyst. Its etiology, however, is conjectural, and whether it should be classified as congenital or acquired would depend upon the authority consulted. The history would, however, offer the possibility of the cyst having an acquired origin. The severe pneumonia at fifteen years of age could have been followed by epithelization of an abscess cavity, since all of the patient's symptoms seem to date from this time. This can, of course, be only speculation for the patient had no x-rays prior to that time.

Case No. 2 seems to definitely fulfill a congenital or developmental origin for it consists of a lesion having bronchial elements that does not communicate with the bronchial tree and is similar to the congenital bronchiogenic cysts of the mediastinum described by Adams and Thornton.[18]

Case No. 3 is a typical alveolar cyst but its etiology is also speculative. The presence of an associated bleb in a singer who undergoes strenuous respiratory activities would seem to point to the possibility that this lesion also arose from a bleb or bulla as has been described by Ackerman and others, and should therefore be classified as acquired.

SUMMARY

The literature on cystic disease of the lung has been briefly reviewed and three case histories described. This is a lesion which is becoming more frequently recognized and in which definitive surgery has been established as the treatment of choice. The classification of the disease and the theories of its etiology, however, still vary considerably with different authorities.

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The use of a thing is only a part of its significance. To know anything thoroughly, to have the full command of it in all its appliances, we must study in on its own account, independently of any special application. —*Goethe*

Immunity and Resistance in Poliomyelitis

A BRIEF RÉSUMÉ OF THE LITERATURE

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A résumé of some old and some new information on poliomyelitis is timely inasmuch as physicians will be called on during the coming months for advice concerning active immunization. Many questions will arise. Some can be, and others cannot be answered. In this brief review I have attempted to summarize some of the opinions on immunity and resistance in poliomyelitis, in a hope that they will be useful in discussions by physicians in the practice of medicine.

HISTORICAL NOTE (1)

Poliomyelitis has undoubtedly occurred in antiquity, and yet periodic outbreaks have been clearly recognized only during the last eighty years. During the last fifty years many have studied the disease. Heine, Medin, and others described the clinical patterns which we recognize at the present time. The essential changes in the central nervous system (CNS) were described by Charcot and by Rissler and by Wickman. Landsteiner and Popper reproduced the disease in monkeys and it was subsequently established that the infectious agent was a filterable virus. Wickman's studies, made during early epidemics, indicated that the disease was infectious and transmissible from person to person. He recognized minor illnesses associated with paralytic poliomyelitis in members of the same household, and considered them to be abortive forms of poliomyelitis. This much had been recognized in 1910.

At this time poliomyelitis entered into a historical era (1910-1930) compounded in error. It was a time when it was considered that poliomyelitis was spread by droplets laden with virus, and the portal of entry was the nasopharynx. It was a time when immune serums were prepared and were found unavailing in the treatment of paralytic poliomyelitis. It was a time when the strict neuronotropism of the poliomyelitis virus was established. Reports appeared in this country and in Sweden that poliomyelitis virus was present in the feces of paralyzed children.[1,2,3]

Many changes occurred during the last twenty years. Old concepts were abandoned for new. Concepts on epidemiology were sharpened. The presence of virus in the gastro-intestinal tract was reconfirmed. Its persistence in the intestine for months after onset of illness, and the potential risk of fecal carriers in populations at risk were recognized. The virus was detected in the oropharynx during the early days of a paralytic attack. Specific antibodies were often found at the onset of paralysis, providing confusion as to the relationship of these antibodies to the disease. Ecologic studies, seeking an extra-human reservoir of virus incriminated the blow fly and certain other species as carriers, if not a means of dissemination of poliomyelitis virus. Antibodies were detected in the serums of cattle and dogs. But the virus was never found in the body tissues of any animal, excluding man. Three immunologically distinct types of poliomyelitis viruses were identified. The virus was detected in the circulating blood—and notions of strict neuronotropism had to be revised. Vaccination tried earlier by Kolmer[4] and Brodie[5] was reconsidered, and brought at the doorstep of clinical field trial.

CHANGES ENCOUNTERED IN THE DISEASE PATTERN

In the Jeremiah Milbank report[1] it is stated—"No circumstance in the history of poliomyelitis is so baffling as its change during the last two decades of the nineteenth century from a sporadic to an epidemic disease." The older literature contains references to localized outbreaks but there is not a single reference to any widespread epidemic. What is the explanation? Was there a change in the virus? Or was there a change in the susceptibility of children since they in particular bore the brunt of the attack?

There is no convincing evidence that poliomyelitis suddenly acquired virulence permitting it to provoke clinical illness. Nothing exists to indicate that the infection was caused by a virus introduced into a highly susceptible population. Indeed, the fact that children and not adults were attacked most often, suggests that adults had acquired immunity as a result of previous experience with poliomyelitis virus. It is possible that a mutant strain possessing enhanced virulence emerged and suddenly became dominant in a population of viruses heretofore almost entirely harmless in human beings, but it is not likely.

What changes occurred among people? It was a period of changes; some of these are still in evolution. There were *social changes,* among them the trend toward smaller family units. There was a migration of people from the town and country to the city. There were changes in *concepts of hygiene.* Pasteur's microbes led to the Listerian era and thence

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to community health. In the cities, slops and dung were disposed of by underground sewers. It was not perfect. Privies and other local deposits of ordure remained, as they do today in some of our urban and suburban areas. There were also changes in family hygiene. Houses were screened against flies. Efforts were put forth to stamp out infestation of homes and industrial places of rats and insects. The individual became aware of the danger of germs and personal hygiene probably reached as high a level during the last half of the nineteenth century as it had for the Greeks and Romans at the height of their respective civilizations.

The first large epidemics appeared in Sweden, and shortly thereafter in North Central Europe and in the United States. Widespread outbreaks soon appeared in north and south temperate climates. By and large, peoples living in the tropical and semitropical countries were spared outbreaks of epidemic proportions, but sporadic cases appeared more or less constantly. Soldiers from temperate climates on entering the tropical areas were not spared from poliomyelitis although very few cases were seen among the native population. It is assumed that the rebirth of community hygiene, chiefly in the form of modern water and sewage disposal plants, has commanded a fee best calculated in loss of immunity to poliomyelitis because less and less virus was available for immunization during infancy, and for periodic reinforcement during later life. A contrasting situation exists in certain tropical and semitropical areas where it is difficult for an informed person, and practically impossible for an uninformed person, to escape fecal contamination. Hence, rapidly acquired latent immunization, and constant reinforcement of the antibody mechanism, protect the people in these areas from frank clinical forms of poliomyelitis.

Two other changes will be noted, namely, (a) in age groups attacked by poliomyelitis, and (b) in rural versus urban attack rates. At the beginning, infants and young children were almost always the victims of paralysis. Over the past thirty-five years there has been a gradual inclusion of more teenagers and young adults. In the early years of the twentieth century there were more older children and young adults attacked in rural areas. At the present time the age incidence in town and country are not different. This interesting shift in age distribution is not well understood. It is of serious portent because young adults, in comparison with children, have a more severe illness, are apt to have bulbar involvement, recuperate less rapidly, and the death rate is two or three times higher.

The clinical attack rates in rural and suburban populations have exceeded those observed for the more densely populated sections of cities. Forty years ago these changes were striking enough that Lavender, Freeman, and Frost[1] considered "the proportionately greater rural prevalence has been so constant as to be unmistakably due, not to mere chance, but to some fundamental law." An explanation given to these findings has been that latent immunization proceeds faster in urban that it does in rural areas, providing in the latter accumulations of susceptibles, and hence proportionately more at risk of the paralytic event. There are other factors related to means of virus spread including the possibility of extra-human reservoirs of poliomyelitis virus in the animal kingdom. During recent years in some sections of the United States the urban and rural attack rates are no longer very different.

In summing up, it is clear that many changes have occurred in the disease pattern of poliomyelitis since 1880. Some evidence suggests that these changes are related to host-susceptibility, chiefly because of rapidly changing concepts in socio-economic conditions and that these have had an impact on family and community life. It would appear probable that with improved sanitation, and the consequent removal of the largest source of virus in sewage, that latent immunization proceeds at a slower rate, and that there is a discontinuous distribution in age-specific attack rates with a continuing accumulation of susceptibles available for infection with the virus. Others have considered that resistance may be related to either (a) genetic factors of susceptibility, or (b) seasonal alterations in the intracellular milieu which facilitate invasion and disease.

THE PATTERN OF POLIOMYELITIS IN THE INDIVIDUAL

The diagnosis of paralytic poliomyelitis is not difficult, and seldom challenges the acumen of the clinician. It is quite difficult, if not impossible, to make the diagnosis prior to the onset of signs related to the central nervous system. The pre-paralytic phase of illness has been described, but is not widely appreciated. It consists of fever, malaise, sore throat, diarrhea, and abdominal pain, lasting two to four days. There may then be a comparatively symptom-free interval of several days before paralysis intervenes. It is well recognized that many individuals experience mild prodromata, and that the intervening paralysis appears apparently without antecedent signs or symptoms. Further, many individuals who have the pre-paralytic type of illness never have subjective evidence of paralysis, and it is now ascertained that these illnesses occurring in an epidemic area, particularly in relationship to associate cases, are abortive forms of poliomyelitis. The ratio of the paralytic and non-paralytic forms have been estimated as being from 1:1000 to 1:20.

THE PATTERN OF POLIOMYELITIS IN THE HOUSEHOLD

The existence of minor illnesses which undoubtedly represented infection with poliomyelitis virus was suspected since the early studies of Wickman, Caverly, and others.[1] Definite proof that these illnesses

were poliomyelitis was obtained by Trask, Paul, and their co-workers,[6] and in recent years by Francis, and by Wenner and their colleagues.[7, 8] In certain families, particularly those with many young children, it is the rule rather than the exception to obtain a history of non-paralytic illness in several members associated with a paralyzed sibling. Proof that these illnesses are caused by poliomyelitis virus has been obtained by the direct isolation of virus from the stool, and by the emergence of type-specific antibodies in the blood stream of these individuals.

In the past, as now, it has not always been easy to determine whether one of the family members introduced the virus into his household, or whether the family group was infected from some common source. Our family studies have led us to the following conclusions. First, the onset of illness among familial associates in relation to the index case occurred three or four days before or after onset in the paralyzed patient. Considering the mean incubation period to be about twelve days,[9, 10] this means that members of this family unit were infected at a common source. It is our opinion that a food product contaminated by poliomyelitis virus is the logical source. Admittedly proof for this assumption, excepting possibly for milk-borne outbreaks, is hard to obtain. A study by Zintek[11] in which it was shown that virus appeared simultaneously in the feces of all members of a household associated with a paralyzed child add support to the assumption that parasitism of the alimentary tract occurs presumably from virus acquired at a common source.

Multiple household infections are not common to all families. As children become older and migrate into extra-familial groupings it is logical that isolated cases can occur. We have studied two such families in which only one member, each in his early teens was the only member in the family demonstrated to carry virus. These individuals in daily contact with their family associates failed to infect them, indicating to us that infection with poliomyelitis virus is not readily acquired by droplet infection. Unfortunately, these studies were done several years ago when simple, inexpensive tools for serum antibody levels were not available. The antibody levels before, during, and after exposure are essential in support of our assumptions. We are engaged in obtaining this information at the present time.

There are instances when secondary cases may appear within affected households. A sibling playmate of a neighbor's child acquired his infection from the latter. The sibling in the prodromal period infected his brother. It is our opinion that infection may occur as a result of oral ingestion of virus presumably originating in feces containing poliomyelitis virus. Consider the readiness with which pinworm infestation occurs in children and adults in a household! It has been, and continues to be fairly easy for infected adults to disseminate enteric disorders. How simple then is it for a child to pass feces containing poliomyelitis virus from his fingers to the oral cavity of others who play or care for him.

THE PATTERN OF POLIOMYELITIS IN THE COMMUNITY

A low paralytic attack rate occurs in poliomyelitis. In severe outbreaks it is uncommon to have over-all urban rates exceeding 4/1000 population; it is not uncommon to meet rates higher than this in rural communities. The low rates are somewhat misleading in that they fail to be concerned with rates of infection, a subject on which more information is needed. It would appear that low paralytic rates may be attributed to the following: (a) a high index of infection with a low index of disease, and a resulting high index of immunity in the general population, (b) a high index of infection in stratified segments of the population with corresponding segmental immunity which is not nearly so comprehensive as measles or influenza in the total aggregate of people attacked, or (c) a high index of infection in the population at risk, the paralytic event occurring as a result of an anatomical accident.

The ratio of subclinical to clinical infections is considered to be a function of age.[12] Serologic surveys indicate that the rate of antibody acquisition is not constant since the distribution of antibodies in 5-year age groups varies considerably in different geographic areas. In some urban areas of the United States at age 10 (years) about 50 per cent, and at age 20 about 75 per cent of individuals acquire antibodies against one or more of the known types of poliomyelitis viruses. Were these data to be translated to the country as a whole, acquisition of virus by the population at risk would be fairly rapid and comprehensive.

If one assumes that the ratio of inapparent and apparent infection is constant, one cannot be other than perplexed at the irregularities in the geographic location of cases occurring in urban areas. The studies made by Francis et al,[7] and by Wenner et al[8] point out that there is a tendency to have aggregation of cases around infected households. Francis has said, "The major concentration of poliomyelitis virus is in the families, including adults, and in intimate groups in which the disease appears. . . ." The available evidence lends support to the notion that the velocity of spread of poliomyelitis virus is slow, and that over the summer and autumn months irregular foci of cases (and those inapparently infected) appear and gradually converge on each other, providing what would appear to be uniform dissemination of virus when actually a small and limited fraction of the population has been involved. The slow radial movement of poliomyelitis has been noted. In Casey's study the rate was 0.1 mile per day; in Paul's study it was 0.5 mile per day.

These observations suggest that only a part of the population, chiefly at risk, namely children under 10 years of age, have been infected with poliomyelitis virus, and that a large and relatively unknown segment remains unaffected during any given season and awaiting subsequent attack. Our studies suggest that the velocity of spread is slower than measles, for example, because the virus requires a medium of transfer similar to that of enteric diseases, and that the infection rates are lower than measles leaving behind many more susceptibles, some of whom will become immune by virtue of living in an environment periodically and sporadically seeded with virus.

THE PATTERN OF IMMUNITY IN THE INDIVIDUAL

Recurrent attacks of paralytic poliomyelitis occur; the chance of reoccurrence is infrequent. It was thought that an attack of poliomyelitis conveyed an appreciable immunity to a new infection. The serologic response, often used to indicate immunity, was rather disturbing because antibodies were present in the patient's serum virtually at the time that paralysis made its appearance. Further, no appreciable increase occurred during convalescence. Hence it was difficult to know whether poliomyelitis antibodies were present because of the present infection or were the result of a previous experience with the virus or a related antigen. In a small proportion of the cases there was a relatively slow rise of neutralizing antibodies over a period of several months.

At the present time some of these difficulties have been solved. It is recognized that illness caused by poliomyelitis virus occurs about a week prior to onset of central nervous system involvement. Moreover, viremia occurs during this period in a substantial number, if not all, of the people who experience primary infections. Hence neutralizing antibodies are in the blood stream at the time when injury to the central nervous system is manifest. The recognition that there are three distinct immunologic types of poliomyelitis viruses, and that they appear to be mutually exclusive in the specificity of the antibody response, offers an explanation why antibodies aren't found in some patients—their serums were tested usually with a heterotypic strain of virus. Only in recent years have serums obtained from patients been tested with the patient's virus.

The acquisition of antibodies against the three known types increases with age. At age 5, for example, 20 to 40 per cent of children in various areas of the United States have antibodies against one type, while at age 18, about 40 per cent have antibodies to all three types. Many of these individuals have never been ill with paralytic poliomyelitis. Those who have had paralytic poliomyelitis have had but a single attack. What this means is that infection with the other heterotypic viruses was unrecognized, which is probable, or that there is antigenic overlap among certain strains, which appears at the present time somewhat improbable.

In summary, paralytic poliomyelitis conveys homotypic immunity. Such immunity is evidenced by resistance to the disease (but not necessarily to infection with another type) and by the appearance of homotypic humoral antibodies which persist for years. A large number of abortive infections occur with poliomyelitis virus and obviously convey an immunity durable enough to prevent the paralytic form of the disease.

THE PATTERN OF IMMUNITY IN THE COMMUNITY

In regard to community epidemiology we remarked on the slow velocity of infection, and the focal accumulation of cases in households and in intimate groups. Unfortunately, at this time there is limited evidence from serologic studies in support of, or in opposition to, these observations. A large number of serologic studies have been made in several communities. Before the tissue culture methods became available the type 2 (Lansing) virus was used because tests could be made on a statistically sound basis using mice. A large amount of information exists in regard to the distribution of type 2 neutralizing antibodies. In Baltimore, the emergence of Lansing antibodies was observed to occur during the summer months. By the time an individual is 10 years of age, and if he resides in the Eastern Health District of Baltimore[13] he has acquired type 2 antibodies. In Cario, Egypt antibodies are found in 70 per cent of three year olds, and in all by the time children are four years of age.[14] Among Alaskan Eskimos antibodies were absent in individuals less than 20 years of age, and were present in practically all individuals of 20 years or older.

Samplings in regard to the presence or absence of antibody have been made in various geographic areas and in various age groups and with regard to socioeconomic factors. Although these data seem to indicate universality of infection at a given age in a population, they have failed to provide an index of velocity of infection. The only pertinent report on the aspect is by Melnick and Ledinko, whose studies in Winston-Salem began before and continued beyond an epidemic period. By following the development of neutralizing antibodies in 200 children, they showed the emergence of antibodies against type 1 and type 2 viruses, and none against type 3 poliomyelitis virus. On the basis of these data, they were able to determine the ratio of subclinical infections to paralytic cases. These varied somewhat with age, ranging from 175:1 for infants less than a year of age, to 95:1 for those 10 to 14 years of age. It would appear from this study that in any given epidemic year about one-fourth of the population under 15 years of age becomes immunized. Since latent immunization occurs between epidemics some

of the remainder are being continuously added to the immune group. On this basis poliomyelitis has a rather sweeping inclusion of susceptibles in epidemic years, particularly in regard to the specific type of virus responsible for the outbreak. At this time it is necessary to recall that during a number of outbreaks several types may be isolated in a given community.

PATTERNS DESIGNED FOR THE CONTROL OF POLIOMYELITIS

The available data indicate that in a population many are at risk of infection, but few are at risk of paralysis. The risk obviously diminishes with age, although this is not a constant, since older age groups are attacked somewhat more frequently in the last thirty years. The occurrence of paralysis in poliomyelitis is an intriguing problem in pathogenesis, and at the present time all of the reasons for its occurrence are not known.

Three approaches have been considered in immunization against poliomyelitis. The approaches are based, in part, on facts discussed earlier in this paper. They include (a) a "killed" virus vaccine, (b) active virus vaccine, with or without administration of antibody, and (c) an avirulent virus vaccine.

The formalin-treated triple vaccine is an example of the first type, and is the kind of vaccine which is currently being made ready for the field vaccination trials. The use of killed virus vaccines has disadvantages in respect to the development of immunity and the endurability of the immunity. The premise on which vaccination with formalinized virus is based, is that (a) the humoral antibody level need not be high (i.e. about 1:64) in order to block the passage of poliomyelitis into the central nervous system, and (b) the augmentation of the antibody response will occur periodically as a result of re-infection with all three types of poliomyelitis viruses. If the premises are correct, vaccination with formalin-inactivated viruses may turn the tide away, not from infection with poliomyelitis viruses, but from the risk of the paralytic event.

The formalinized vaccine has been studied rather extensively in Allegheny County, Pennsylvania. The antibody response using the polyvalent vaccine in individuals who do not have antibody is low in magnitude (i.e., about 1:16 to 1:64). The response in individuals who do have antibody is swift and the level of antibody reaches high levels (i.e., about 1:1000 or better). The important issue in the field trial is whether antibodies acquired by non-immune individuals is of sufficient level to prevent the 1:100 to 1:1000 risk of paralysis.

An issue of importance is whether vaccination with formalin-treated virus will create an enduring immunity. Will vaccination with "killed" virus be an annual event among children? The answer isn't known. If re-vaccination becomes necessary what are the risks involved in the repetitious use of killed virus grown in monkey epithelial cells? The answer to this question isn't known either, although available information indicates that the vaccine has no nephrotoxic effect as currently used. Several of us have raised the query: What effect will the administration of monkey kidney cell debris have on the development of Rh antibodies? It is believed that monkey tissue and red cell antigens are different and that the risk of sensitization in Rh negative girls is improbable. The belief has not yet been examined in the test situation, and the answer is not available at this time.

Immunization with active virus together with gamma globulin has a number of disadvantages. First, passive antibody ties up the virus and active immunity is unlikely to follow parenteral injection of virus. A much more serious objection is that antibody-virus mixtures are not always inactivated and active virus may produce infection in the presence of antibody. From the point of view of practicability of such type of vaccination, it is not safe.

Active immunization may follow oral administration of virus in human beings. Koprowski[15] and his associates have fed a type 2 strain of rodent-adapted virus to children. Following oral administration of virus there was a significant rise in type 2 antibodies. None of the children suffered any ill effects.

A number of laboratories are searching for avirulent strains of poliomyelitis viruses. There is some evidence to indicate that they occur. The adaptation of strains to hamsters and then to chick embryos[16] has resulted in a variant which has lost much but not all of its original virulence. The passage of certain strains, using special techniques in tissue culture, has modified strains so that their behavior does not resemble the effect of the parent strain in experimental animals. None of these strains is ready for test in human beings. There is sufficient promise in the work already done to urge further studies in the effort to obtain modified poliomyelitis viruses, avirulent for monkeys, but on oral or parenteral administration capable of providing immunity to poliomyelitis in human beings.

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Rupture of the Colon Secondary to Muscular Strain

REPORT OF TWO CASES

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Rupture of the colon secondary to muscular strain is rare and results in a severe abdominal catastrophe. It is thought that it occurs usually as a result of some underlying pathology. Rupture of the bowel under an intact abdominal wall has long been a subject of interest to the surgeon, mainly because of the acute severity of the condition.

Wilensky and Kaufman[8] reviewed the literature up to 1936 and found forty-two cases of ruptured intestine due to muscular effort reported at that time. They reported one additional case. In the majority of these cases the rupture occurred secondary to a hernia and involved in most cases the small bowel. It is interesting to note that some of the early writers thought that increased intraperitoneal pressure could not, in itself, result in intestinal rupture. It has been shown that adhesions and agglutinations of the intestines predispose to rupture after severe straining by inhibiting the motility of the bowel. Berman *et al*[1] in further discussing bowel perforation with hernia as a secondary cause stress the importance of this condition in industrial medicine. In one of their two cases reported, compensation was allowed while the second one was in arbitration at the time the article was written. Several cases of rupture of the colon due to compressed air have been reported by writers.[2, 3, 4, 5, 6] This type of rupture is brought about by the introduction of compressed air into the rectum—usually during some "horse play" or prank. Prior to the use of antibiotics the mortality rate of these cases was quite high. We are all acquainted with the fact that perforation of the colon can be brought about while the patient is getting a barium enema or by the introduction of the colon tube. Rupture of a diverticulum of the colon is not uncommon, as is perforation in ulcerative colitis.

Weinstein and Roberts[7] in 1952 reported one case of spontaneous perforation of the colon without a pathological condition. Up to that time only one other similar case had been reported according to their article. Their patient perforated while having a bowel movement. Qvigstad[9] reported a case of perforation of the transverse colon in a four day old infant. An autopsy was done and microscopy revealed a defect in the muscular layer at one side of the perforation. He thought that the pathogenesis possibly could have been a congenital anomaly.

The following two cases are being reported mainly because of the rarity of the condition. The first case, with the perineal stoma following a Lynch operation for carcinoma of the rectum would questionably have some underlying pathology, while the second case could definitely be secondary to some long standing pathology.

CASE NUMBER ONE

Mr. C. L. P., a 58-year-old, white male was admitted to St. Joseph Hospital, November 13, 1951, with the chief complaint of severe pain in the lower abdomen. At 5:00 A. M. that morning the patient had gotten out of bed and went to the bathroom to have his usual morning bowel movement and while straining at the stool he developed severe acute pain in the lower part of the abdomen and became unconscious. He gradually regained partial consciousness and was brought into the hospital, traveling a distance of approximately 75 miles.

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The past history of the patient revealed that on October 10, 1950, the patient was operated on by Doctor Claude Tucker, of this city, for carcinoma of the rectum. A Lynch operation was done at that time. The pathological diagnosis was Grade II adenocarcinoma of the rectum with metastasis to regional lymph nodes.

Upon admission the patient was semi-conscious, nauseated and vomiting. He appeared to be in shock. His pulse was somewhat weak and was 100 per minute. His temperature was 101.8°. Examination of the abdomen revealed moderate distention with generalized tenderness. There was considerable muscle guard over the whole abdomen with marked rebound tenderness. The perineal stoma was examined and nothing unusual was found. The admission diagnosis was probable acute intestinal obstruction.

Soon after admission a flat plate of the abdomen was done, but this revealed no evidence of any intestinal obstruction. The admission blood count revealed 4,420,000 red blood cells, 13 grams of hemoglobin, 9,850 white blood cells, with 70 segmenters, 1 stab, 2 eosinophils and 27 lymphocytes. The urinalysis was essentially normal. He was given intravenous fluids and antibiotics, with other supportive therapy, and was later taken to the operating room. At operation a right rectus incision was made and the abdomen opened. On examination of the abdomen no evidence of any recurrent carcinoma was found. The patient was very obese, so considerable adipose tissue was encountered in the abdominal wall and in the abdomen. On opening the abdomen a large amount of fecal material was found in the abdominal cavity, which appeared to be coming from the left lower abdominal gutter. A perforation, approximately one-half inch in length, was found posterior to the bladder, in the hollow of the sacrum. Due to the adipose tissue and the position of the lesion, it was impossible to see the area, but the perforation could be felt. In view of this, a transverse colostomy was carried out and a stab wound was made in the left rectus area, through which rubber drains were brought out, draining the pelvis, and the left gutter. Due to the shortness of the colon it was necessary to bring the colostomy out of the upper portion of the incision. The colostomy was a simple loop colostomy. A mushroom catheter was placed in the proximal portion of the colon. Another drain to the right side of the pelvis was brought out the lower portion of the incision. After routine closure the patient was placed in a lithotomy position and a rubber tube drain was placed into the hollow of the sacrum through an incision made posterior to the perineal stoma. He left the operating room in fair condition and was given transfusions.

This patient was given large doses of antibiotics, mainly penicillin, and all drainage tubes were removed in due time. He progressed nicely until the 19th of November, when he had a severe coughing spell and eviscerated. He was then taken back to the operating room where a secondary closure of the eviscerated wound was carried out. Following that procedure he did well and on November 28, 1951, he was returned to surgery and the colon was divided completely, leaving a functioning and nonfunctioning colostomy. The two stomas were approximately three inches apart. Following that he did well and was dismissed from the hospital December 2, 1951. Since dismissal from the hospital the patient has been in good health, has been doing his work, which has consisted of routine farm work and driving a tractor. He has not been seen, but in a recent written communication he stated that he has felt well and is well satisfied with the abdominal colostomy.

CASE NUMBER TWO

S. S., age 42 years, white male, was admitted to St. Joseph Hospital on January 29, 1954. The afternoon and evening prior to admission he had been working hard and had been lifting some Butane tanks which weighed approximately 150 pounds. He had worked until 11:00 P. M. that night and had gone home and gone to bed. At approximately 2:00 A. M. he was suddenly awakened with severe acute lower abdominal pain. He vomited several times and his general condition became worse. He finally called his family doctor and then was admitted to the hospital that afternoon with severe generalized abdominal pain. His past history revealed that he had had a ruptured appendix at the age of nine, at which time the appendix was not removed, but was drained. He was very ill at the time and the drain was left in for several days. He had had no serious difficulty and no surgery other than that at the age of nine.

On examination this patient was acutely ill. The abdomen revealed moderate distention and generalized tenderness, which was worse in the right side. There was considerable muscle guard and rebound tenderness over the whole abdomen. Rectal examination revealed nothing unusual. The admission diagnosis was intestinal obstruction with peritonitis. A flat plate of the abdomen was taken in the supine and upright positions and a diagnosis of probable mechanical intestinal obstruction, involving both jejunal and ileal segments was made. On admission the blood count revealed 5,200,000 red blood cells, 14.5 grams of hemoglobin, 15,850 white blood cells with 77 segs, 8 stabs, 15 lymphs. The urine was essentially normal except for 8 to 10 pus cells per high power field. He was given supportive treatment including intravenous fluids and 500 cc. of whole blood. He was started on antibiotics, mainly penicillin and dihydrostreptomycin.

He was taken to the operating room where the abdomen was opened through a right rectus incision

and upon opening the abdomen considerable free pus was found and aspirated and generalized peritonitis was evident. On examination of the abdominal viscera the pathology was found in the region of the cecum. No appendix was present, but there was apparently a thinned area in the wall of the cecum where the appendix had been and through this thinned out area was a one-half inch perforation. This was closed with catgut sutures and a stab wound was made to the right of the incision and two rubber drains were brought out through that wound. These drained the region of the cecum and the right abdominal gutter. Routine closure was carried out and the patient returned to his room in fair condition. Large doses of penicillin and dihydrostreptomycin were given the patient. A Levine tube was left in the stomach for four days and the drains were removed after five days. His convalescence was smooth and uneventful. He was dismissed on February 12, 1954 and has been seen at intervals in the office. He has done well and when last seen, a month ago, he had no complaints.

DISCUSSION

Rupture of the colon secondary to muscular strain is a rare condition and should be kept in mind when a patient is seen with severe peritonitis, which develops following acute severe abdominal pain. The seriousness of the condition cannot be over-emphasized and the value of large doses of penicillin and dihydrostreptomycin cannot be underestimated.

SUMMARY

1. Review of literature has been presented.

2. One case of ruptured colon following severe straining at the stool has been presented. This patient had had a Lynch operation for carcinoma of the rectum three years previously. At the last operation no evidence of any recurrence of the carcinoma was found.

3. Another case has been presented in which perforation of the cecum followed heavy lifting and straining. The perforation was apparently in the location of the base of the appendix, which had sloughed away when the patient was a child.

4. The severity of the condition has been stressed.

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An Error in Blood Sugar Determinations

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The diagnosis of diabetes mellitus applied to the individual patient is so important in the latter's economy as regards his way of life and the practical matters of life insurance, etc., that it behooves us to use the most accurate diagnostic methods available for this designation.

We have been impressed by the work of Mosenthal[1] in a review describing the discrepancy between true blood sugar and total reducing substances in the blood. The popularly used Folin-Wu[2, 3] method for blood sugar determines the latter whereas the Somogyi[4] technique is supposed to reveal the former. Obviously, if a method is available for the doctor's office and the average hospital laboratory to measure only true blood sugar, it is to be preferred over the Folin-Wu procedure. Therefore, we have set out to determine whether the Somogyi method is technically feasible, accurately reproducible (including recoverability of added glucose), whether after removal of blood glucose by yeast fermentation the Somogyi method reads zero, and whether by the fermentation technique the difference between the total reducing substances and the true blood sugar can be predicted by the Somogyi method.

Having studied these factors, we have determined a number of fasting and non-fasting blood sugars in diabetics using both methods, and for comparison have repeated the determinations on several of the same patients to check for individual variations in non-glucose reducing substance in a particular diabetic over a period of time.

In addition we have documented numerous glucose tolerance tests using both methods dually.

MATERIALS AND METHODS

The Somogyi modification described by Nelson[6] uses a solution of $Ba(OH)_2$ which is unstable, so we chose the method originally suggested by Somogyi:[4]

A. Blood Filtrate
1 cc. oxalated blood dissolved in 7 cc. of H_2O
Add 1 cc. Sol I and mix
With continual shaking add 1 cc. Sol II
Filter
Sol I is 10% $ZnSO_4 \cdot 7H_2O$
Sol II is 0.5 N NaOH
} These must be titrated against each other so that 10 cc. Sol I added to 50 cc. of H_2O will turn phenolphthalein pink with 10.8 cc.—11.2 cc. of Sol. II.

B. 2 cc. of this blood filtrate in a Folin-Wu sugar tube
2 cc. of alkaline copper tartrate solution
Mix with lateral shaking
Boil 8 minutes in boiling water bath
Cool to room temperature
Add 2 cc. phospho-molybdic acid sol and mix
Place in boiling water for 5 minutes
Dilute to 25 cc. with distilled water and mix
Read in Leitz colorimeter set at 520.

It is to be noted that part B is the same as part B in the Folin-Wu method. The strategic reagent is the neutral zinc, which causes precipitation of the non-glucose reducing substances which are not precipitated by tungstic solution as used in the Folin-Wu[2] procedure which follows:

A. Blood Filtrate
Into a flask place 2 cc. of oxalated blood
Add 16 cc. of N/12 sulfuric acid
Mix
Add 2 cc. of 10% sodium tungstate
Mix well
Filter through Whatman filter paper No. 40 (filtrate should be clear)

B. Same as Part B in Somogyi method

Method of yeast fermentation:[6, 7]

Dissolve a cake of commercial yeast in about 30 cc. of distilled water. Transfer to centrifuge tubes. Spin down (10 min.—3000 rpm). Pour off supernatent fluid. Wash this four times. Make up to 20 per cent solution with distilled water. Pour 10 cc. of this solution into 3 centrifuge tubes. Spin down. Pour off supernatent fluid. Add 6-10 cc. of Folin-Wu filtrate to one tube. Add 6-10 cc. of Somogyi filtrate to a second tube. Add distilled water to the third tube to serve as a blank. Stir each one with a glass stirring rod until the suspension is even. Set aside for 10-15 minutes at room temperature. Spin down.

Two cc. of the supernatent fluid from each centrifuge tube is placed in a Folin-Wu sugar tube. Two cc. of copper tartrate solution is added to each one. Proceed as in B above to determine the reducing substances left in the filtrates.

Note. If the yeast was sufficiently washed, the blank will read negative. If it does not read negative, it can be substituted for the blank already in the colorimeter, and the determinations can then be read on the colorimeter.

Table 1 lists four determinations in which a known amount of glucose was added to blood where the glucose content had been determined by both Folin-Wu and Somogyi methods. Recoverability was within 3 milligrams per cent using the Somogyi technique.

TABLE 1 (see text for explanation)

Folin-Wu	*Somogyi*	*Somogyi with 100 mg.% glucose added*
133 mg.%	107 mg.%	208 mg.%
208	183	280
305	290	390
308	248	345

Table 2 indicates parallel blood sugar determinations using both methods and the readings for both methods on the resultant filtrate after yeast fermentation had been carried out. It will be noted that all examples after fermentation read zero with the Somogyi procedure, with the exception of one 2 milligram reading. It is also readily apparent from the table that the artifact in the Folin-Wu procedure with regard to non-glucose reducing substances varies from 10 to 33 milligrams. Conversely, the Somogyi technique allows accurate prediction of the amount of non-glucose reducing substance since the original difference between the methods checks well with the amount left in the Folin-Wu filtrate after fermentation.

TABLE 2

Folin-Wu	*Somogyi*	*Folin-Wu after yeast fermentation*	*Somogyi after yeast*
103 mg.%	82 mg.%	18 mg.%	1 mg.%
212	192	19	0
315	280	33	0
200	188	10	2
224	193	27	0
128	107	19	0
118	86	26	0

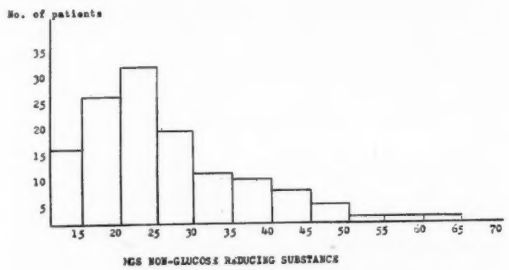
To check the reproducibility of the Somogyi method, we determined results in duplicate on 10 patients. The readings were never more than 3 milligrams apart.

Table 3 lists 96 blood sugar determinations using the two methods in parallel, and it can be seen that the lowest amount of non-glucose reducing substance was 10 milligrams and the greatest 63 milligrams per cent.

TABLE 3

Folin-Wu	*Somogyi*	*Difference*
110 mg.%	87 mg.%	23 mg.
133	115	18
345	305	40
92	82	10
230	202	28
103	73	30
110	79	31
148	124	24
92	70	18
268	230	38
224	193	31
128	96	32
140	109	31
137	110	27
165	137	28
100	64	36
240	224	16
165	144	21
212	188	24
103	75	28
188	170	18
255	210	45
103	75	28
105	85	30
107	55	42
107	60	47
323	260	63
208	150	58
212	155	57
148	98	50
140	90	50
98	55	37
212	150	62
110	65	45
110	75	35
103	52	51
305	290	15
280	248	32
202	160	42
128	92	36
255	235	20
212	198	20
110	79	21
92	64	28
103	79	23
88	60	28
165	150	15
133	107	26
107	90	17
117	92	25
208	183	25
103	70	33
305	290	15
280	248	32
260	240	20
167	154	13
100	79	21
137	107	30
275	260	15
212	192	20
315	280	35
212	190	22
112	92	20
153	140	13
200	188	12
110	85	25
280	268	12
153	135	18
200	170	30
107	80	27
100	75	25
96	82	14
110	82	28
153	117	36
113	96	17
103	83	20
110	92	18
335	315	20
197	181	16
110	88	22
100	85	15
113	100	13
188	165	22
103	82	21
335	323	12
113	88	25
198	183	15
175	153	22
224	193	32
128	107	21
100	79	21
100	75	25
185	130	55
110	87	23
116	86	30
148	124	24

Graph 1 reveals 131 patients with amounts of non-glucose reducing substance increasing in increments of 5 mg. The vertical bars indicate the number of patients, the horizontal bars being the milligrams of non-glucose reducing substances. A glance will show that there are 16 patients with a discrepancy between the two methods of from 10 to 15 mg., whereas 26 revealed a difference of 15-20 mg., 32 a difference of 20-25 mg., 18 a difference of 25-30 mg., 11 a difference of 30-35 mg., et cetera.



GRAPH 1

Table 4 lists the fasting blood sugar of 7 diabetics with blood sugars taken over a year's period of time. We were interested to discover if, for a given period, the quantity of non-glucose reducing substance stays approximately the same. It is evident from this table that such is not the case, there being as much as 51 milligrams difference in one patient from time to time. We have not determined whether the non-glucose reducing substances stay the same over any one period of time for a given level of blood sugar.

TABLE 4 (See Text)

Patient	*Folin-Wu*	*Somogyi*	*Difference*
Mrs. L	345 mg.%	305 mg.%	40 mg.
	212	188	24
	323	260	63
	305	290	15
	305	290	15
	275	260	15
	280	268	12
Mr. N	230	202	28
	140	90	50
	202	160	42
	224	193	32
Mrs. S	110	79	31
	212	192	20
Mrs. G	153	117	36
	268	230	38
	255	210	45
	167	154	13
	280	248	32
	280	248	32
	200	170	30
Mrs. G	224	193	31
	198	183	15
	212	155	57
	208	183	25
	200	188	12
Mrs. D	140	109	31
	110	75	35
	133	107	26
	113	100	13
	148	124	24
Mr. M	116	86	30
	110	88	22
	112	92	20
	92	64	28

Table 5 gives the results of glucose tolerance tests with parallel determinations and indicates the milligrams of non-glucose reducing substances found in 7 patients, only 1 of whom was diabetic.

TABLE 5

Patient		*Folin-Wu*	*Somogyi*	*Difference*
Mrs. S	Fasting	103 mg.%	75 mg.%	28 mg.
	1 hr.	96	85	11
	2 hr.	79	55	24
	3 hr.	85	70	15
	4 hr.	92	73	19
Mr. B	Fasting	92	47	45
	1 hr.	110	52	45
	3 hr.	60	35	25
	4 hr.	88	50	38
Mr. D	Fasting	101	56	45
	½ hr.	140	100	40
	1 hr.	124	75	49
	2 hr.	96	72	24
	3 hr,	60	39	21
	4 hr.	75	47	28
Miss. McC	Fasting	110	73	37
	1 hr.	193	144	49
	2 hr.	183	165	49
	3 hr.	128	104	24
	4 hr.	137	93	44
Mr. S	Fasting	117	82	35
	1 hr.	133	114	19
	2 hr.	82	58	24
	3 hr.	117	93	24
	4 hr.	100	70	30
Mrs. F	Fasting	103	82	21
	1 hr.	160	140	20
	2 hr.	102	82	20
	3 hr.	86	68	18
	4 hr.	85	66	19
Mrs. H	Fasting	101	76	25
	1 hr.	120	100	20
	2 hr.	107	85	22
	3 hr.	90	70	20
	4 hr.	88	70	18

COMMENTS

To discover if the above techniques are practical, we have carried them out in our office laboratory, and it has become apparent that there is no more labor involved in the Somogyi technique than in the more-commonly used and, we believe, out-moded Folin-Wu procedure. The criteria mentioned at the beginning of this paper, that is, method of determination, reproducibility, determination of true blood sugar, seem to be fulfilled.

It should be stated that we have not observed the Folin-Wu procedure to label a patient falsely diabetic, remembering that the standard for the Folin-Wu method is a fasting blood sugar below 120 mg. per cent (or at the end of the second hour of a glucose tolerance test), whereas that for the Somogyi technique is similarly below 100 mg. per cent. Nevertheless, it seems to us entirely possible that through the years, with the discrepancy between the two methods being as variable and as high as it occasionally develops, such an error is ultimately inevitable.

One might also comment on the current dispute between those who advocate very strict regulation of the diabetic and those doctors who teach a freer technique in that with as much as 60 mg. of artifact occurring in the Folin-Wu method, this being the method almost universally used at present, normoglycemic fasting blood sugar is actually dangerously low in some patients.

SUMMARY AND CONCLUSIONS

In summary, we believe that the Somogyi method should be adopted for the routine determination of blood sugars. It is conveniently adaptable to the average office and hospital and considerably more informative than the Folin-Wu procedure now in common use. We have found that the reducing substance determined by the former procedure is entirely removed by fermentation with yeast, and that from 10 to 63 mg. of reducing substance may remain after glucose is removed by fermentation. Further, this amount of reducing substance is reported as glucose in the Folin-Wu technique.

Periodic fasting blood sugar determinations in diabetics have revealed a variable and inconstant amount of non-glucose reducing substance ranging from 12 to 57 milligrams per cent. Also glucose tolerance tests reveal that during a four hour determination there may be as much as 49 milligrams per cent variation between glucose and total reducing substance in the blood.

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Science seeks truth and discovers rightness. Religion seeks righteousness and discovers truth. Both have acquired knowledge of creative and destructive ways, and both point the same way of right living. —*William G. Patten*

PRESIDENT'S PAGE

DEAR DOCTOR:

Yesterday, today and tomorrow converge in this era of speed. The dreams of yesterday are distorted in the frenzy of today and are thrust into tomorrow's reality. Medicine illustrates this platitude both vertically and in a lateral plane, both through its scientific achievement and its sociological evolution.

Yesterday, in the dawn of medical discovery the physician found new means for preventing disease and for arresting its progress. He traveled long weary hours in the darkness and through mud to minister to those in need, but he walked a free man unafraid of his future, unfettered by governmental regulations and controls.

Today his vertical progress is expected and demanded by the public. What was considered a miracle cure a short time ago is now taken for granted. But with this opportunity for increasingly greater service comes a strangling lateral control. The ideal of individual achievement is being crushed out in favor of mediocrity, in favor of the average. Today conformity is the rule and society is the king.

Tomorrow those influences will be united and woven into a single pattern. Its effect will be determined by what we do today, in our professional career as well as in our citizenship. If ever we had a need for clear thinking and decisive action in the preparation of a future that day is now. As physicians we perhaps have an understanding of our duties but as citizens we must waken to a new responsibility. One, among the many opportunities in this direction grows out of our right to vote. May we not neglect this expression of good citizenship in November.

Yours,

Murray C. Eddy, M.D.

EDITORIAL COMMENT

A History of the Society

On February 10, 1959 The Kansas Medical Society will become one-hundred years of age. This notable date is just four and one-half years away and plans are now being formed for a fitting commemoration of this event.

This Society was chartered by the Territorial Legislature before Kansas became a state. Even at that time, the hardy immigrant pioneer physicians who incorporated the Society envisioned an organization that would improve the practice of medicine for the purpose of better serving the people of this new land.

Early transactions are reviewed with a smile where an occasional enthusiast tells his colleagues that the end of all medical discovery is at hand, or in such homely soft spots where everyone's dues were forgiven because the secretary lost the ledger, or in the record of spirited differences of professional opinion as for instance, a discussion of the scientific possibilities of mesmerism.

Not funny at all are the discussions of needs for higher standards. From the very earliest meetings appear pleas for a license law whereby physicians would be required to show some educational qualifications before being permitted to practice in this state. Nearly one-hundred years ago they appeared before the legislature asking for quarantine laws, for vital statistics records and for the power to enforce sanitary measures in an effort to avert the ever threatening epidemics of cholera, smallpox and diphtheria. They begged first the Board of Regents and then the legislature repeatedly for a chair of medicine at Kansas University.

They worked then as does the Society today for such improvements as will provide for a healthier population. In the early records they expressed pride for having attained a remarkable life expectancy of 40 years. By 1900 they were rejoicing that this had been raised to 49 years just as the Society today expresses pleasure that this figure stands at 69 years. And then, just as in the case today, they were looking ahead toward greater improvements in the future.

This Society has grown great because of its uncompromising insistence upon maintaining the highest ideals of medicine. Its unwavering acceptance of the responsibility to be of service to the public has been a continuing challenge. This forward looking view has kept the Society active and has kept it young which, be it hoped devoutly, shall always be its course.

However, a backward glance is not completely in vain, especially upon the approach of a centennial. Here the tragic revelation becomes apparent that history has not been preserved. The forefathers of this Society were so engrossed with affairs of the day at hand, that the past has all but been obliterated.

Gone are priceless experiences of how medicine was practiced in the past. Gone are the biographies of the pioneers in Kansas medicine. Departed from memory are the circumstances upon which great decisions were made.

As the centennial approaches the Committee on History hopes to prepare a record of The Kansas Medical Society. They most hopefully request assistance in gathering data for this project. Every recollection of past experience will be of interest. The biography of an early member will be appreciated. Samples of early instruments, the story of the use of drugs in the 19th century, the organization of county societies, early text books will all be of value.

This committee urgently requests any member who has access to any information, however slight, concerning medicine in the early days of this state, to send it to The Kansas Medical Society, 315 West Fourth Street, Topeka, Kansas. Similarly if anyone can suggest where such material may be located, that information will be of value. It would be most appreciated if a wealth of data could be accumulated now so the history can be prepared by 1959, in time for the centennial. Your personal help can make this project successful.

Federal Health Programs

PART III

This installment completes a review of federal participation in health programs. As stated in Part I, see the July, 1954, JOURNAL, the federal government will have spent during this fiscal year more than one and three-quarters of a billion dollars in some sixty separate agencies dealing with health. The previous sections discussed some of these programs and the remainder appear below.

The Department of Labor expected to spend during the fiscal year closing June 30, 1954, $8,960,000, mostly in two fields. The Bureau of Employees Compensation accounts for about $8,500,000. Its service is roughly to federal employees what Workmen's Compensation is to the states. There are more than two million persons covered and benefits include medical, hospital and burial expenses. The second is the Health and Safety Program with a budget of just under a half million. This includes such programs as for re-employment of the physically handicapped and the promotion of industrial safety.

The Foreign Operations Administration spent $24,500,000 for health out of a total budget of more than $118,000,000 to aid backward countries. Last

year the health fund was spent as follows: Six million for Latin America, seven million for the Near East and Africa, and eleven million for South and Southeast Asia, to mention only the major contributions.

The Department of Interior spent $27,258,600 for health under three divisions. The Bureau of Indian Affairs received $21,400,000 to operate 59 Indian hospitals, for contract health services and including $551,687 for administration and salaries. The Bureau of Mines spent $5,060,000 of which $3,700,000 was for mine inspection, $850,000 for investigations of accidents and rescue work, and $510,000 for explosives testing and research. The third is the Alaskan Mental Health Program with a budget of $798,600.

The Department of Commerce spent $621,000 for health of which half is used by the Bureau of Standards to test such things as hearing aid batteries, substitutes for blood plasma, heart pumps and artificial kidneys, etc. The other half goes to the Civil Aeronautics Administration to carry out the medical portion of this authority's flight safety program. Fourteen medical officers supervise the annual physical examinations of commercial and private pilots, a total of some 160,000 who pay for their examinations. This does not come from federal funds.

The Department of the Treasury spent $2,790,000 on narcotic control, about 90 per cent of which went for salaries. The Department of Justice spent $1,326,000 under the Bureau of Prisons for medical and dental care for some 18,000 prisoners in 27 federal penal institutions.

There follows a listing of independent offices not directly attached to any other bureau or department. The National Science Foundation used $8,000,000 of which half was used to correlate research and services of other agencies and half for research grants.

The Federal Civil Service Administration had $26,650,000 earmarked for health and medical stockpiling, including $250,000 for salaries and travel.

The Atomic Energy Commission spent $26,565,000 as follows: $10,376,700 for research on the effects of radiation; $8,036,300 for general medical research including radioisotopes; $4,788,900 for biophysics; $2,833,100 for cancer research; and $530,000 for fellowships and special training. The above is just medical work out of a total A.E.C. budget of $1,057,781,000.

The Health Resources Advisory Committee used $91,000, and the National Advisory Committee to Selective Service spent $265,000.

Medical Care in the Panama Canal Zone cost $5,448,600 for the operation of four hospitals with a total of 1,400 beds, six outpatient medical clinics, two dental clinics, quarantine service, insect control programs and others.

Medical work of the Federal Trade Commission accounts for one-fourth of its total budget or about one-million dollars to administer food, drug and cosmetic controls.

The Commission on Intergovernmental Relations operates with a budget of $500,000 to study the services of all the agencies mentioned in this report. This 25-man commission has until September 1 of this year to complete its fact finding program.

The Commission of the Executive Branch of the Government consists of twelve members under Herbert Hoover. It is interested in promoting efficiency and in reducing government competition to free enterprise. This commission has $500,000 and is required to complete its survey by May 31, 1955.

Federal Employees Health Programs spent $6,000,000 last year for health services to keep federal employees on the job. Most of this money was spent for pre-employment examinations, for clinics to treat on-the-job illnesses and accidents, and for such care, as for example, the giving of insulin, if such is recommended by the family physician.

This three-part review was taken from a report issued by the American Medical Association's Washington Office in the interest of providing information to the medical profession upon federal participation in health programs. A considerable portion of these services is performed within the states and often with state financial support. This series will be continued in future issues to show where Kansas receives federal support and how such funds are spent.

A.M.A. Annual Session

Many physicians have read the proceedings of the recent meeting of the American Medical Association which was held in San Francisco in June of this year. A number of Kansas physicians journeyed to the West Coast to take part in the meeting. Some presented scientific exhibits and others read a paper. Delegates representing The Kansas Medical Society fulfilled their responsibilities and still other physicians took advantage of the clinical sessions and the many other opportunities afforded at that meeting.

Noticeably absent during the business session of the House of Delegates was the usual confusion and debate which generally arises over the many resolutions presented. Although some seventy-five resolutions were acted upon, various committees had spent considerable time throughout the year studying the problems and reporting at the meeting. Specific instructions on many of the resolutions were given by state societies to their delegates prior to the meeting

which was another factor contributing to the smooth functioning of the meeting. For those who have not had access to information on the meeting, the following is a condensed version of some of the important action taken by the A.M.A.

Several resolutions by various state medical societies were introduced regarding osteopathy and medicine. The Committee of the Board of Trustees which submitted a report to the A.M.A. House of Delegates in June, 1953, suggested at that time that osteopathy be removed from the "cultist" classification and that doctors of medicine be permitted to teach in osteopathic schools. The principle criticism of this report was that the committee had to rely on indirect evidence concerning the nature and scope of education in osteopathic schools. The committee reported at the recent meeting that it had proposed to The American Osteopathic Association that a special committee be established to visit schools of osteopathy to determine the quality of medical education provided. The A.M.A. approved of this action.

The House of Delegates reconfirmed their stand on "fee splitting, rebating or payment of commissions in any form whatever." This problem has been studied the past two years by the Committee on Constitution and By-Laws of the A.M.A. and after a lengthy discussion in reference committee, their report was adopted.

The stand of the A.M.A. regarding veterans medical and hospital care remained unchanged. The A.M.A. will continue to seek legislation which would limit medical care in Veterans Administration and other hospitals to:

A. Veterans with peacetime or wartime service whose disabilities or diseases are service-incurred or aggravated.

B. Within limits of existing facilities to veterans with wartime service suffering from tuberculosis or psychiatric neurological disorders of nonservice connected origin, who are unable to defray the expense of necessary hospitalization.

It was again suggested that veterans with nonservice connected disabilities who are unable to defray expense for such care can receive attention from local personnel and facilities.

Smaller hospitals (under 100 beds) will receive attention during the coming year by the A.M.A. The Council on Medical Education and Hospitals was asked to study and set up a system of standardization for smaller hospitals. Those in small hospitals find it difficult to maintain the standards set by the Joint Commission on the Accreditation of Hospitals.

Dr. Edward J. McCormick, immediate past president of the A.M.A. urged physicians to adopt average fee schedules on an area or regional basis to overcome a large number of complaints by patients in regard to fees. This would also enable the patient to determine the ultimate cost of the medical service he seeks.

The seal of acceptance of voluntary health insurance plans will be discontinued by the A.M.A. Because of varying state laws, it is feared that the use of the seal might give the public an erroneous impression. It is suggested that any person purchasing or recommending any health insurance plan might examine the plan in the light of A.M.A. standards and principles which will be available as a guide.

Dr. Walter J. Martin of Norfolk, Virginia, was installed as President of the A.M.A. and Dr. Elmer Hess of Erie, Pennsylvania, was unanimously elected to the office of President-Elect at the final meeting of the House of Delegates on June 24, 1954.

BOOK REVIEW

Endemic Goiter, The Adaptation of Man to Iodine Deficiency, by John B. Stanbury, M.D., Gordon L. Brownell, Ph.D., Douglas S. Riggs, M.D., Hector Perinetti, M.D., Juan Itoiz, Ph.D., Erique B. Del Castillo, M.D., Harvard University Press, Cambridge, Massachusetts, 206 pp., 53 figures, $4.00.

This is the report by a distinguished group of investigators on their physiological studies of the iodine starved thyroid gland as found in Mendoza Province of Argentina, where it has been reported that four fifths of the men and women of the province have visible tumors of the neck. The method of study included the use of tracer doses of radioactive iodine, with the measurement of uptake and excretion. The effect on the distribution of iodine in the body from administering additional iodine, desiccated thyroid, methimazole, and thyrotropin, was also studied. Mathematical calculations based on several assumptions gave results reasonably close to the observed values. In a relatively short space one is acquainted with the frontiers of the goiter problem.

The iodine content of the drinking water in Mendoza was found to be 2.1, 3.0, and 2.0 micrograms per liter, which was compared with 27.8 and 18.2 micrograms per liter for tap water in Boston on two determinations. No reference is made to the book by McClendon, *Iodine and the Incidence of Goiter.* Since these studies were completed the Argentine Government has made the sale of iodized salt compulsory. Although the iodine content of the drinking water in much of the midwest is reported to be even less than that found in Mendoza, we still have our choice of plain or iodized salt at our grocery. If we choose the iodized, one gram of the salt per day contains enough iodine to prevent goiter.—*K.Y.*

Supplement to Roster

In June 1953, this Society with the Kansas State Board of Medical Registration and Examination published a Roster of Kansas Physicians. During the interval since that date, numerous changes have occurred to render it comparatively obsolete, so elsewhere in this JOURNAL may be found a list of names which when used with the previously published Roster will again make it usable.

Certain explanations may be necessary for an understanding of how this supplement might be used. This new listing includes members only. Information on nonmembers would be obtained only with some difficulty so no attempt has been made to correct changes as they affect names which appear in lower case print in the Roster.

1. Members—To Be Added, lists names of physicians, now members of this Society who have joined since June 1953. They may have recently moved to this state, or may have been previously listed in lower case type.

2. Members—Address Changes, lists those members (in capital letters) from the 1953 Roster whose present address differs from the previous printing. Since office addresses are given only for physicians in the larger cities, these are listed if the office address is changed. Otherwise, in all the smaller towns the name appears only if the member moved to a different community from that listed in 1953.

3. The section headed "Alphabetized by Towns" merely regroups all the names appearing under "Members to Be Added" and "Members—Address Changes" according to their present location. It should be recalled that this is not necessarily a complete listing of physicians in any named community. This records only the changes that have occurred since the last Roster was published and should be used in connection with it.

4. Deletions is a record of members whose names may be taken off the previous Roster. They are deceased or have moved out of the state and in one or two instances may still be in the previously listed location. However, they are not members of The Kansas Medical Society at the present time and for the purposes of the supplement have therefore been removed from the listing.

The Supplement, therefore, is not a new Roster, but merely an attempt to bring the other up-to-date. It lists only those changes that affect members and will become useful only in connection with the previous publication. In 1953 each member received a copy. Some are still available and may be purchased with the supplement at a cost of $1.00. Should this be desired, they may be obtained through The Kansas Medical Society, 315 West Fourth Street, Topeka, Kansas.

New Members

Aronson, Gerald ..... Columbia, S. C.
Ashley, E. Vernon ..... Bushton
Atwood, M. Dale ..... Kinsley
Baeke, John O. ..... Overland Park
Bayles, Hugh G. ..... Fredonia
Bayles, Spencer ..... Kansas City
Benkelman, Ward E. ..... Polson, Montana
Bill, Robert O. ..... Topeka
Birdsell, John E. ..... Topeka
Bly, Chauncey G. ..... Kansas City
Bodmer, Robert A. ..... Coldwater
Brooker, Robert M. ..... Topeka
Brooks, R. D. ..... Madison
Buddrus, David J. ..... Prairie Village
Budetti, Joseph A. ..... Wichita
Burgess, Arthur P. ..... Oswego
Calderwood, Barbara ..... Phillipsburg
Christensen, Marion D. ..... Kiowa
Custer, Harry R. ..... Colby
Delaney, W. M. ..... Topeka
Diacon, James L. ..... Wellington
Diehl, Antoni M. ..... Kansas City
Diehl, Leonard R. ..... Osborne
Dittemore, James H. ..... Belleville
Dobratz, Robert A. ..... Chetopa
Dreyer, Richard ..... Salina
Ens, Peter D. ..... Hillsboro
Evans, Mary E. ..... Kansas City
Fatland, John L. ..... Council Grove
Firminger, Harlan I. ..... Kansas City
Fitzpatrick, Martin J. ..... Kansas City
Fowler, W. L. ..... Concordia
Frederickson, Evan L. ..... Kansas City
Gendel, Evalyn S. ..... Auburn
Griffith, John K. ..... Effingham
Guggenheim, Paul ..... Topeka
Gunter, Carl G. ..... Quinter
Haley, Jack A. ..... Hanover
Hamm, Orville L. ..... Gardner
Hassard, George H. ..... Sedan
Heasty, Alfred ..... Conway Springs
Heffner, Edward A. ..... Hutchinson
Hege, John H. ..... Sunflower
Heisterman, Herman W. ..... Quinter
Hoff, Donald E. ..... Wichita
Hooker, Lyle T. ..... Osawatomie
Hull, Norman E. ..... Hays
Hutchinson, Glen C. ..... Hays
Ivy, H. B. ..... Meridian, Mississippi
Jackson, George W. ..... Topeka
Jastram, R. M. ..... Minneapolis, Minnesota
Jenkins, Neal M. ..... Salina
Ketterman, Grace H. ..... Kansas City
Kiser, David M. ..... Overland Park
Kittle, C. Frederick ..... Kansas City
Kramer, Lee F. ..... Cherryvale

Laaser, William E. ..... Kansas City
Laurens, Henry ..... Salina
Lessenden, C. M., Jr. ..... Topeka
Lothman, T. L. ..... Enterprise
Lowry, Ray F. ..... El Dorado
Lund, Leonard C. ..... Osawatomie
McCann, William ..... Olathe
McClymond, Robert C. ..... Walton
McGonigle, Lester E. ..... El Dorado
McGovern, James L. ..... Wellington
McGuire, George E. ..... Wichita
McGuire, John W. ..... Neodesha
Madison, Willard A. R. ..... Nortonville
Magee, Charles Raymond ..... Marion
Mastio, George J. ..... Ulysses
Miller, William Robert ..... Axtell
Mueller, Adolph Reginald ..... Leavenworth
Neis, Harry B. ..... Olathe
Nesselrode, John H. ..... Kansas City
Nutting, Harry C. ..... Emporia
Olson, Erwin T. ..... Newton
Orrison, William W. ..... Minneola
Osborne, J. O. ..... Ness City
Owensby, Lindell C. ..... Concordia
Page, Vale ..... Plainville
Parker, David Findley ..... Tonganoxie
Parker, Joseph W. ..... Burlington
Pearce, Lunetta M. ..... Sunflower
Plowman, Carl W. ..... Jewell
Pogson, George W. ..... Pittsburg
Powell, Charles ..... Columbus
Preheim, Delbert Victor ..... Newton
Rhoades, Gordon Howard ..... Halstead
Rice, David R. ..... Moundridge
Ridlon, Albert M. ..... South Whitley, Indiana
Rottersman, William ..... Topeka
Rowlett, Jack G. ..... Paola
Schraer, Paul ..... Concordia
Schwartz, Eugene ..... Dodge City
Schweinfurth, James P. ..... Wichita
Siler, Eugene T. ..... Hays
Smith, James D. ..... Satanta
Spanos, William J. ..... Kansas City
Stanley, Rex C. ..... Paola
Struxness, Erling B. ..... Hutchinson
Sullivan, Henry B., Jr. ..... Shawnee
Sweeney, John E. ..... Topeka
Tarnower, William ..... Topeka
Taylor, James A. ..... Muncie, Indiana
Terrill, Robert S. ..... Topeka
Thompson, Victor J., Jr. ..... Topeka
Throckmorton, Marion ..... Halstead
Tikellis, I. J. ..... Lawrence
Todd, Richard N. ..... Kansas City, Missouri
Tozer, Richard C. ..... Topeka
Treger, Donald M. ..... Bremerton, Washington
Vogt, William L. ..... Champaign, Illinois
Voorhees, Carroll D. ..... Leavenworth
Weldon, Thomas A. ..... Perry
Wenner, Herbert A. ..... Kansas City
Williams, Donald L. ..... Garden City
Williamson, Paul ..... Osawatomie
Wilson, Vernon E. ..... Kansas City
Wood, Robert G. ..... Coffeyville
Woods, Hugh J. ..... Smith Center

Members—Address Changes

Aleshire, Irma ..... Iowa City, Iowa
Artman, John C. ..... Kearney, Nebraska
Bair, Albert E. ..... Wichita
Bantleon, V. H. ..... Kansas City
Belisle, R. C. ..... Hays
Bell, Bertha E. ..... Ottawa
Bice, Francis J. ..... Wakeeney
Bishop, Francis E. ..... Massapequa, New York
Blevins, Walter E. ..... Liberal
Bonfanti, Albert ..... Junction City
Bowen, Murray ..... Bethesda, Maryland
Brownlee, William ..... Mission
Calkins, Larry L. ..... Kansas City
Campbell, Charles A. ..... Phillipsburg
Case, Laurel G. ..... Wichita
Claypool, J. Gordon ..... Narberth, Pennsylvania
Coffey, Roy B. ..... New York, New York
Coffman, James H. ..... El Dorado
Coyle, John F. ..... Panama City, Florida
Critchfield, T. W. ..... Seattle, Washington
Crockett, C. A. ..... Arlington, Virginia
Demand, J. W. ..... Long Beach, California
Dimond, E. Gray ..... Overland Park
Dunagin, Jack A. ..... Topeka
Edmiston, R. H. ..... Americus
Edwards, E. M. ..... Mt. Rainier, Maryland
Edwards, R. W. ..... West Los Angeles, California
Ehrlich, Karl A. ..... Oakland, California
Enna, Carl D. ..... Kansas City, Missouri
Ewing, T. D. ..... Larned
Fairchild, John P. ..... Fort Sam Houston, Texas
Fairchild, Robert C. ..... Mission
Fall, N. B. ..... Colorado Springs, Colorado
Floyd, Glen ..... La Jolla, California
Friesen, Florence ..... Hesston
Funk, Edward D. ..... Prairie Village
Garst, R. J. ..... Joplin, Missouri
Germann, Donald R. ..... Kansas City
Gianakon, Harry G. ..... Kansas City
Good, Wendell L. ..... Mission
Gootee, Joseph E. ..... Topeka
Grider, W. H. ..... Altadena, California
Gundle, Sigmund ..... Kansas City, Missouri
Gyarfas, W. J. ..... Duarte, California
Haffner, V. B. ..... Montevallo, Alabama
Hands, S. V. ..... Wichita
Harsha, W. N. ..... Oklahoma City, Oklahoma

Hays, A. D. ..... Baxter Springs
Helwig, G. F. ..... San Jose, California
Henry, Victor G., Jr. ..... Ft. Leavenworth
Hildyard, V. H. ..... Minneapolis, Minnesota
Hogan, T. W. ..... Terre Haute, Indiana
Hopp, Ralph L. ..... Ann Arbor, Michigan
Howard, Richard R. ..... Slidell, Louisiana
Hughes, Robert D. ..... Marysville
Huscher, Gladys ..... Concordia
Johnson, Charles H. ..... Mission
Johnson, L. D. ..... Kansas City, Missouri
King, E. R. ..... Cleveland, Ohio
Kridelbaugh, William W. .... Albuquerque, N. M.
Lance, Raymond W. ..... Arma
Laury, David G. ..... Olathe
Law, Findley ..... Bird City
Lockett, George R. ..... Concordia
McCoy, Charles T. ..... Hutchinson
Maier, Edwin R. ..... Rochester, Minnesota
Marrs, E. A. ..... Colorado Springs, Colorado
Martin, John N. ..... Chillicothe, Missouri
Maser, G. R. ..... Mission
Miller, Jack P. ..... Yakima, Washington
Mitchell, A. D. ..... Kansas City, Missouri
Montgomery, Charles ..... Roswell, New Mexico
Myers, Ben L. ..... Santa Rosa, California
Nevitt, R. R. ..... Iola
Nice, William ..... Topeka
Nickell, Wendell K. ..... San Angelo, Texas
Peck, J. H. A., Jr. ..... San Diego, California
Pederson, Arnold M. ..... Plainville
Peiper, Warren S. ..... Mitchell, S. D.
Pennington, Katherine ..... Baltimore, Maryland
Pottorf, Mildred M. ..... Wichita
Preston, Ralph R. ..... Topeka
Purinton, Lew W. ..... Norfolk, Virginia
Robison, Leonard J. ..... Irving, Texas
Roccaforte, Daniel S. ..... Salina
Scimeca, Salvatore A. ..... Wichita
Selzer, Donald W. ..... Aitkin, Minnesota
Sirridge, Marjorie S. ..... Fort Riley
Sirridge, William T. ..... Fort Riley
Smith, Carl M. ..... Clermont, Florida
Snyder, Z. H. ..... Hays
Stacey, Harley ..... Oklahoma City, Okla.
Sterrett, Preston ..... Humansville, Missouri
Tetzlaff, Fred M. ..... San Francisco, California
True, Otis H. ..... Kansas City, Missouri
Voth, Harold W. ..... Larson AFB, Washington
Walters, Orville S. ..... Topeka
Wartman, Calvin ..... Bremerton, Washington
Weber, Clarence J. ..... Salina
Weed, Randal ..... St. Joseph, Missouri
Weeks, Vernon L. ..... Fargo, North Dakota
Wellman, Garland O. ..... Texas City, Texas
White, R. Burnley ..... Winfield
Wolff, Frederick P. ..... Pratt

Listed By Cities

AMERICUS

Edmiston, R. H.

ARMA

Lance, Raymond W.

AUBURN

Gendel, Evalyn S.

AXTELL

Miller, William Robert

BAXTER SPRINGS

Hays, A. D.

BELLEVILLE

Dittemore, James H.

BIRD CITY

Law, Findley

BURLINGTON

Parker, Joseph W.

BUSHTON

Ashley, E. Vernon

CHERRYVALE

Kramer, Lee F.

CHETOPA

Dobratz, Robert A.

COFFEYVILLE

Wood, Robert G.

COLBY

Custer, Harry R.

COLDWATER

Bodmer, Robert A.

COLUMBUS

Powell, Charles

CONCORDIA

Fowler, W. L.
Huscher, Gladys
Lockett, George R.
Owensby, Lindell C.
Schraer, Paul

CONWAY SPRINGS

Heasty, Alfred

COUNCIL GROVE

Fatland, John L.

DODGE CITY

Schwartz, Eugene

EFFINGHAM

Griffith, John K.

EL DORADO

Coffman, James H.
Lowry, Ray F.
McGonigle, Lester E.

EMPORIA

Nutting, Harry C.

ENTERPRISE

Lothman, T. L.

FORT LEAVENWORTH

Henry, Victor G., Jr.

FORT RILEY

Sirridge, Marjorie S.
Sirridge, William T.

FREDONIA

Bayles, Hugh G.

GARDEN CITY

Williams, Donald L.

GARDNER

Hamm, Orville L.

HALSTEAD

Rhoades, Gordon Howard
Throckmorton, Marion

HANOVER

Haley, Jack A.

HAYS

Belisle, R. C.
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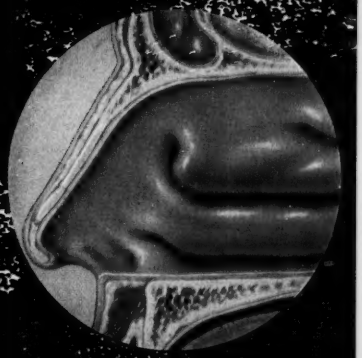

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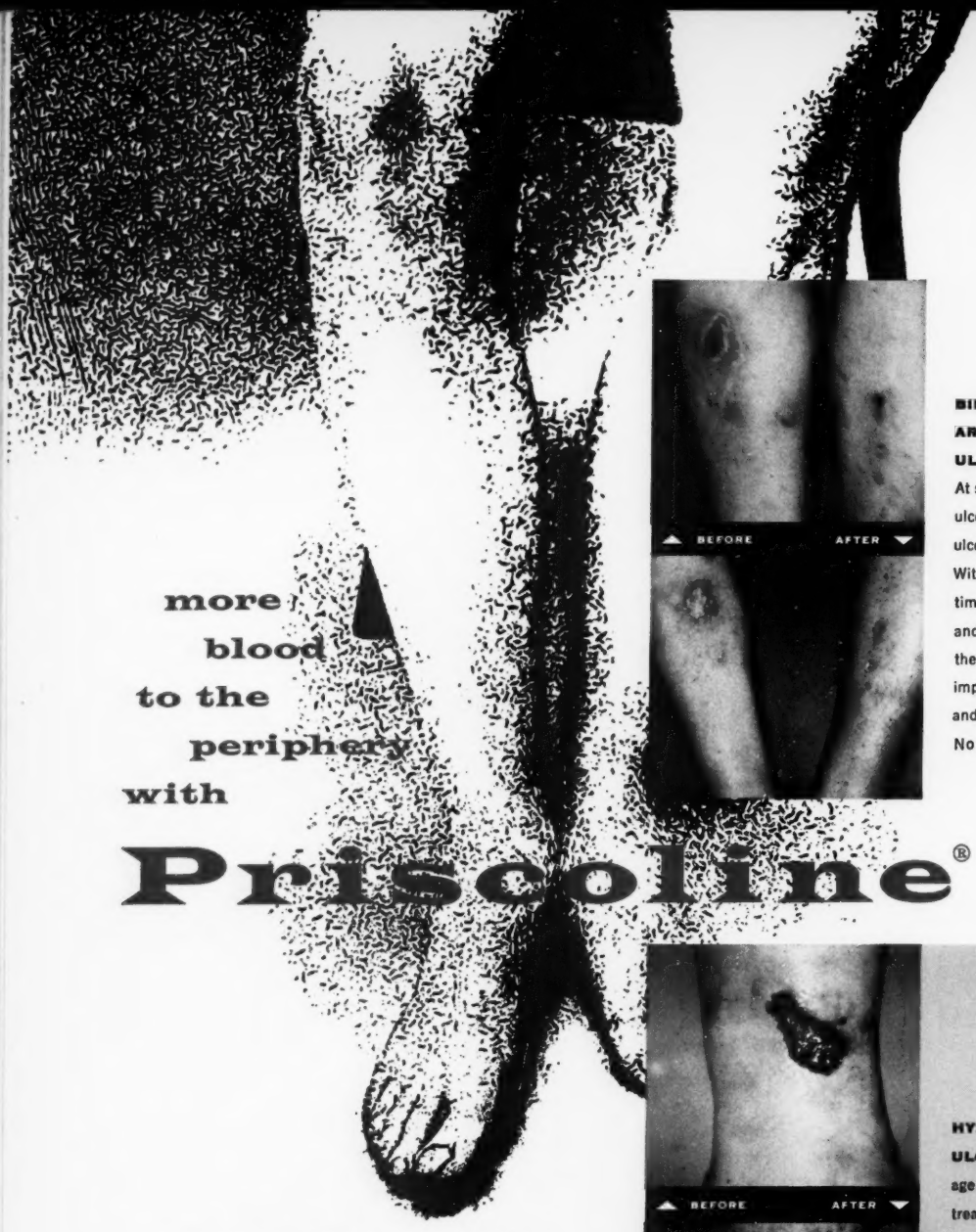

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Spelling Corrections

Attwood, George Arthur ..... Randolph
Glover, Harold Mortimer ..... Newton

Managing Editor Ill

Miss Pauline Farrell, managing editor of the JOURNAL, underwent surgery at St. Francis Hospital in Topeka on Wednesday, August 4. Her physicians report that she is improving rapidly, that she has left the hospital and is now convalescing at home. Her many friends in the medical profession, who will note the absence of her deft hand in the preparation of this JOURNAL issue, wish her a speedy recovery and an early return to her office.

Oklahoma City Clinical Society

The Oklahoma City Clinical Society which had its beginning in 1930 will open its twenty-fourth annual four-day Conference on October 25, 1954.

A large attendance is expected at this ever increasingly popular meeting held in centrally located and easily accessible Oklahoma City. It is interesting to note that at the present time Oklahoma City is rated third in the nation as a convention city.

As in former years, an outstanding program of postgraduate teaching has been arranged. This includes lectures and discussions by sixteen distinguished guest speakers selected from various medical and teaching centers throughout the nation, as well as many Oklahoma City teachers and physicians. Dr. Walter B. Martin of Norfolk, Virginia, president of the American Medical Association, will give an address at the first banquet meeting October 25th. In addition to the general assemblies and panel discussions there will be daily luncheon round table question and answer sessions, and a clinical pathologic conference. The entertainment will include dinner meetings, the annual Clinic Dinner Dance and the Stag Smoker.

A cordial invitation is extended to all physicians who are members of their County Societies to attend this meeting from October 25 through October 28.

Clinicopathological Conference

Case Presentation

Dr. Mahlon Delp, professor of medicine: Dr. Harry S. N. Greene, professor of pathology at Yale, is the visiting professor of pathology at our institution presently and is to be our guest pathologist today. I would hope that our clinicians will be circumspect of their time so that we won't infringe upon the pathologist's time as we have done sometimes in the past. Dr. Steinzieg is going to give us the history.

Dr. Sherman Steinzieg, resident in medicine: The case today is that of a 72-year-old white male who was admitted to KUMC for the first time on June 11, 1953, and who expired on June 14, 1953.

The chief complaint was coma on admission.

Regarding the past history, the patient's family stated that he was apparently in good health until approximately one year prior to admission at which time he developed intermittent bouts of epigastric pain. He also complained at times of a lump in his abdomen. Two months prior to admission the patient became anorexic and developed more pronounced abdominal cramps. He was admitted to another hospital where he rapidly became jaundiced and subsequently developed severe anorexia and dysphagia. He lapsed into coma just prior to being admitted to this hospital. The patient experienced an illness characterized by transient jaundice about five years prior to death. Six months prior to death he underwent prostatic surgery because of difficulty in urination.

Physical examination showed the blood pressure to be 130/75, pulse 80 and regular, temperature 99.6 orally. Pupils reacted sluggishly to light. Bilateral cataracts were present. Fundi were not visualized. The sclerae were icteric. The mouth was edentulous; the tongue was dry; ears, nose and throat were negative. The thyroid was not palpable. There were no unusual cervical masses.

Harsh bronchial breathing was noted in the right posterior lung field and a questionable friction rub was heard. Breath sounds were generally diminished. The lung fields were otherwise clear to percussion and auscultation. The heart was not enlarged to percussion. A_2 was greater than P_2. No murmurs, thrills or arrythmias were noted.

The liver edge was firm and easily palpable three centimeters below the right costal margin. A soft 5 by 5 centimeter mass was noted in the right upper quadrant of the abdomen. The spleen was not palpable.

The extremities were quite emaciated, and the fingers and toes were cyanotic. Deep tendon reflexes could not be elicited. Rectal examination disclosed a slightly enlarged, firm, nodular prostate.

Laboratory examination on June 11 showed that the urine was acid in reaction, specific gravity 1.009, albumin 2 plus, sugar negative, microscopic fields loaded with granular, hyaline and pus casts with 8-10 pus cells per high power field. Blood count was 4.35 million with 12.2 grams hemoglobin; white blood count of 17,150 with 88 per cent polymorphonuclear leucocytes (2 non-filamented), 10 per cent lymphocytes and 2 monocytes. VDRL was negative. Sedimentation rate was 27 millimeters in one hour. NPN 175 mg. per 100 cc., creatine 5.6 mg. per 100 cc., blood sugar 158 mg. per 100 cc. (blood drawn while IV glucose was administered), serum sodium 147 mEq/L., potassium 3.5 mEq/L., CO_2 13.5 mEq./L., chloride 132 mEq/L. Acid phosphatase 1.2. Serum bilirubin, direct, 49.2 mg. per 100 cc., total 70.7 mg. per 100 cc., alkaline phosphatase 54.2, urinary urobilinogen 0.8 milligrams (280 cc. total volume), cephalin cholesterol 4 plus, thymol turbidity 16 units, serum albumin 3.5, serum globulin 4.0, total cholesterol 932 with 10 per cent esters, prothrombin time 25 per cent of normal. On June 12, 1953: NPN 195, creatine 6.8, fasting blood sugar 132, sodium 160, potassium 4.1, CO_2 11.9, chlorides 135.

On admission it was obvious the patient was terminal. However, he was given vigorous supportive therapy, which included blood transfusions, intravenous fluids, antibiotics (penicillin and streptomycin) and 200 milligrams of cortisone intramuscularly. On the night of admission, the patient's temperature per rectum rose to 105.8. He developed a hypotension which was treated with blood transfusions and additional fluids. The following morning the rectal temperature was down to 99.6. However, the patient's condition deteriorated.

On the second hospital day a Levine tube was placed in the stomach for feeding purposes. On the evening of the second hospital day, the rectal temperature again rose to 103.8 and the blood pressure fell to shock levels. In spite of treatment with antibiotics, fluids, blood transfusions and Levophed (nor-epinephrine), the patient's condition worsened

From the University of Kansas Medical Center. Edited by Glen R. Shepherd, M.D., and Mahlon Delp, M.D., from recordings of the conference participated in by the departments of medicine, radiology, surgery (urology) and pathology, and the third and fourth year classes of medical students.

with a quiet death occurring at 8:30 a. m. on June 14, 1953, the third hospital day.

Dr. Delp: Are there questions now concerning the protocol?

Dr. Max Allen, associate professor of medicine: On the second morning, was any difficulty experienced in passing the Levine tube?

Dr. Steinzieg: There was no difficulty about the Levine tube.

Q: The 280 cc. total volume for the urobilinogen determination was representative of a 24 hour output?

Dr. Steinzieg: No, his urinary output was fairly good. It averaged between 1000 and 1500 cc. daily during the three days that he was here.

Q: Was the coma quiet or disturbed?

Dr. Steinzieg: Quiet.

Q: What kind of bowel movements did he have?

Dr. Delp: We have little information concerning the bowel movements prior to his hospitalization. He was having tarry stools the last few hours before his death.

Q: He didn't have tarry stools prior to his hospitalization?

Dr. Delp: We don't think he did have.

Q: Were any spider nevi or distended veins noted over the abdomen?

Dr. Delp: No.

Q: Was there an amine odor of the breath at any time.

Dr. Delp: Yes, he did have an amine odor of the breath from the time of entrance.

Q: Was there any other evidence of hemorrhage?

Dr. Delp: No. This patient was running a fever, he had a temperature of 105.6 and 105.8 within a matter of two or three hours after he arrived here. His temperature curve is pretty typical of what you see on the sheet, sustained but with high peaks. Any other questions? All right, thank you Dr. Steinzieg.

We have one EKG. Stevens, will you demonstrate it for us?

Phillip Stevens, fourth year student:* I was not given the date of this EKG. It shows a rate of approximately 80 with regular sinus rhythm. The most striking features of this electrocardiogram are the slight depressions of ST segments in leads 2, 3, and AVF with a flattening of the T waves in almost all the leads and with prolongation of the QT interval. The diagnosis on the basis of these three findings is hypopotassemia. We cannot rule out a prolonged QT interval on the basis of a hypocalcemia.

Dr. Delp: Any further comments about this, Dr. Dimond.

Dr. E. Grey Dimond, professor of medicine: No.

Dr. Delp: Wilhelm, do you have the x-rays?

* Received M.D. degree in June, 1954.

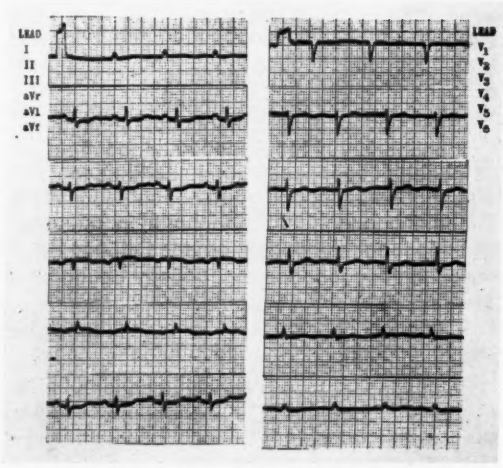


Figure 1. EKG, showing normal sinus rhythm with depressions of ST segment, T wave flattening, and QT prolongation suggesting hypopotassemia.

Paul Wilhelm, fourth year student:* These were taken on the day of admission. The chest film shows that the heart is normal. The costovertebral angles are clear. I can see no pathology of the bony structure. The aorta is prominent which one might expect in a man this age. The bronchial markings are very clear. No pulmonary infiltration is seen.

On the KUB film, the most marked thing is a scoliosis of the lumbar spine and osteoarthritic changes.

* Received M.D. degree in June, 1954.

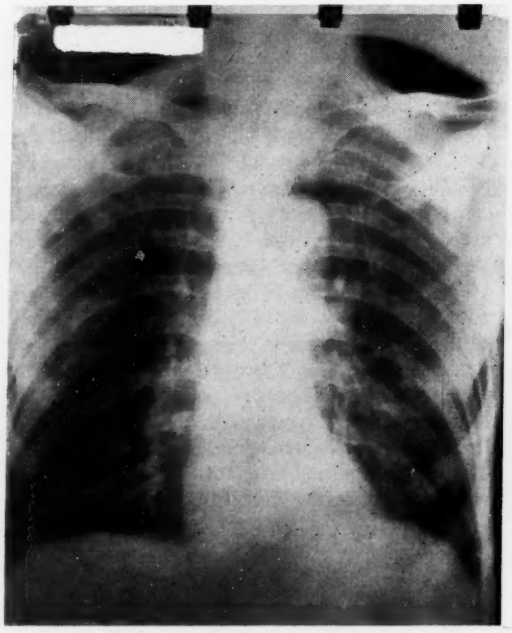


Figure 2. X-ray of chest showing degenerative changes.

Dr. Delp: Dr. Hogan, do you have any comments on the x-ray films?

Dr. Thomas Hogan, resident in radiology: I think the films have poor technique and the detail is somewhat decreased because of that. We interpreted them as essentially normal except for degenerative changes in the spine.

Dr. Delp: You didn't actually think that there was any infiltration in the lung?

Dr. Hogan: No, it wasn't so interpreted.

Dr. Delp: Now, for the purposes of the differential diagnosis and the clinical discussion, I would like to recall certain items in the protocol. First of all, this was a 72-year-old individual. He had been comatose for 24 hours prior to his arrival here. In the history, aside from the coma which his family reported and which we easily observed, he had a loss of appetite and this was emphasized. He had had abdominal pain and jaundice for two months. Whether or not it is significant, I mention that this patient had an episode of jaundice five years prior to this illness. Surgery had been done on his prostate, I assume a transurethral resection, six months prior to this KUMC hospital admission which would make it four months prior to the onset of the present illness.

I saw this man within a matter of minutes after he came in. These features of the physical examination I think were quite obvious. He was jaundiced, comatose, with a mass in the abdomen and certain chest findings which have been recorded in the protocol. There were a number of rather marked elevations and alterations in laboratory findings including the NPN and other features of the liver function profile. Their significance, I think depends upon your own interpretation. Actually I suppose the clinicians are obligated to engage in a rather old academic exercise to determine whether this is an obstructive type of jaundice, a surgical jaundice, and/or a medical type of jaundice. It would seem that there are several possibilities. Lastly of all, I think we are again obligated to attempt to explain the patient's death at the time that it actually occurred. Weigel, will you begin our discussion?

DIFFERENTIAL DIAGNOSIS

John Weigel, fourth year student:* We must do three things: consider causes of coma, causes of this patient's illness and the causes of his death. As

Figure 3. Photograph of gross specimen of tumor, showing opened distended common bile duct with constricting mucosal lesion just above ampulla. A block has been taken from the area of the tumor.

* Received M.D. degree in June, 1954.

Figure 4. Photomicrograph of common bile duct showing infiltration of wall by tumor and its acinar structure.

Dr. Delp has briefly reviewed his symptoms, I won't repeat them.

As to causes of coma, I think we can run very quickly through a good number of these. CVA's and cerebral neoplasms I think we can rule out on lack of history and on the slow onset. Subdural hematomas and middle meningeal artery hemorrhage we can rule out on the history, on the slow onset, and on the physical findings of jaundice in this man's history. This man presented no history of having taken drugs and this was a slow onset. It lasted for a number of days.

This leaves us with a metabolic cause of coma which are several in number. First of all, diabetic coma. Again we have no history of diabetes and we don't have an elevated blood sugar.

We are left with two things, hepatic coma and renal coma. I think I'll confine my discussion pretty much to those two. First of all I'd like to talk a little bit about hepatic coma. This usually begins with a period of excitement or lethargy leading into coma and it's often fairly insidious in onset. This patient had jaundice and fetor hepaticus or amine breath which is again suggestive of liver damage. Oftentimes all other organs of the body suffer.

These patients can present with shock and collapse of the cardiovascular system. This patient had shock. They can present with urinary tract findings such as anuria or oliguria. Probably it is on the basis of shock and failure of the kidneys to do their work. Such patients also present as just a generalized metabolic acidosis which is usually uncompensated. This man had deep respirations which again goes along with the acidotic condition and dry mucous membranes.

Figure 5. Photomicrograph showing higher power view of anaplastic area of the carcinoma.

There have been several mechanisms postulated concerning liver failure. I think one of them is failure of the liver cells to phosphorylate thiamine. Thiamine, of course, is necessary in the tricarboxylic acid cycle and if it doesn't work the patient cannot metabolize the glucose properly. This generally comes out in some of the laboratory work which wasn't done on this patient. Usually there is an increase in lactic acid and pyruvic acid. The urea, the high NPN, again is compatible with renal failure on the basis of hepatic coma. Another mechanism postulated in hepatic coma is intracellular ammonium ion poisoning. It has been shown that a number of patients in hepatic coma will have increased serum ammonia. It is difficult to tell what their intracellular ammonia is but it's known that intracellular ammonia acts as a neurotoxin.

As to the cause of possible hepatic coma in this man, I think we have to think of three things: prehepatic disease, hepatic, or posthepatic disease. I assume on the basis of very high cholesterol and on the basis of the high alkaline phosphatase, high bilirubin and the fact that he had a palpable mass here—which I interpreted as his gallbladder—that he had biliary tract obstruction, probably posthepatic. I think that in cases where you can feel a large gallbladder the odds are that something is blocking the common duct and probably the obstruction is there. Some of these liver tests do show severe hepatocellular damage such as the flocculation test. The alkaline phosphatase elevation could result from intrahepatic blockage. So I think all of these liver tests show us two things: one is that there is obstructive jaundice and the other is that there is a high degree of hepatocellular damage. The urinary urobilinogen finding, which in this man is in the upper limits of normal, is rather confusing but I think that somehow a little bile must have leaked through.

As to the causes of posthepatic biliary obstruction, I want to just review the fairly prominent ones. First of all we have to think of stones as most common. This man did have an episode of transient jaundice five years ago but that's all we have. We don't have an x-ray finding of stones but that doesn't rule it out. But the type of pain, the general lethargy, and the anorexia are not the type of symptoms commonly associated with gallbladder colic. It is also more common in women. This predilection for women applies also to carcinoma of the biliary tract, carcinoma of the gallbladder. That usually occurs in women. It is found 80 per cent or more of the time with gallstones. You wouldn't expect a large, soft gallbladder in that disease.

As far as carcinoma of the pancreas is concerned, we have to think of carcinoma of the head of the pancreas because that's the common cause of the onset

of jaundice in such a patient as this, a man with pain. I think it could be present but there are certain things that would tend to rule it out. I think this patient's other complaints would tend to rule out a primary carcinoma at the head of the pancreas. As far as the tail and body of the pancreas is concerned we'd expect possible diabetes with destruction of the pancreatic gland.

Carcinoma of the ampulla of Vater occurs and again we have a rather insidious onset of generally painless jaundice and also we have bleeding of the GI tract. This man does have bleeding of the GI tract but he did not have a painless jaundice. Metastatic disease to the liver—and I'll talk about this a little more later—is a very possible cause of extrinsic pressure on the common duct which could cause biliary obstruction. Cholangitis commonly follows stasis from any cause. I think the high fever and evidence of liver damage suggests a suppurative cholangitis with extensive destruction of liver tissue.

Renal coma deserves consideration. Its symptoms occur gradually and include lethargy. These patients present with vomiting, anorexia, and apathy. They develop acidosis often with a loss of calcium. They may present as having convulsions. Occasionally they will lose potassium and that could account for this patient's lowered potassium. They can lose potassium by vomiting, by diarrhea as well as by renal mechanisms.

Chloride acidosis can exist in terminal renal disease simply by giving these patients too much chloride, the kidney being unable to handle it. This could account for this man's increased chloride. He did have increased chloride and he had had IV's given. I think the great increase in the NPN, the positive albumin, the cells and the pus casts are all indicative of renal disease. Particularly important, I think, is the creatine being as high as it is. Specific gravity appears to be rather fixed also. The NPN could be due partly to resorbed blood from the GI tract. A prerenal azotemia could be present on that basis but I don't think that would account for the tremendous elevation of NPN which coupled with the other renal findings makes us think of a severe renal disease.

This man had no anuria but he did have casts which make you think of tubular damage, though not lower nephron nephrosis. Cholemic nephrosis is a condition that oftentimes occurs in regurgitation or posthepatic jaundice in which a good deal of bilirubin and bile products are in the blood. It is postulated that bile salts are toxic to the tubules and cause tubular breakdown. There again we see casts, pus cells, epithelial cells.

Hepatorenal syndrome has been discussed by a number of men. Whether such a thing exists or not I don't know. Possibly the shock that occurs in liver failure could account for anuria, oliguria and the signs of renal shutdown as well as the toxic products.

The most common cause of kidney disease in a man over 50 with history of prostatism and prostatic surgery as this man had is pyelonephritis on the basis of obstruction. Obstructive pyelonephritis is roughly 12 times as common as blood-born pyelonephritis. I think he probably developed mild or moderate hydronephrosis bilaterally. I think he probably developed ascending urinary infection with pyelonephritis in both kidneys. This man could have had hypertension on a renal basis and have the symptoms masked by the fact that he was in shock part of the time and on the borderline of shock.

With the history of a nodular prostate and acid phosphatase of 1.2, we just about have to say that this patient had carcinoma of the prostate. I think that that could have metastasized to the liver very easily and caused the obstruction there. In reported cases of carcinoma of the prostate, a good number have metastasis to the lungs and liver.

So my final diagnosis is primary adenocarcinoma of the prostate gland with metastases to the liver causing biliary obstruction. He probably had an ascending suppurative cholangitis destroying a good deal of his liver. I think he had bilateral pyelonephritis with destruction of kidney parenchyma. I think he died of metabolic breakdown or ammonia intoxication.

Dr. Delp: Dr. Mitchell what comments can you make about the acid phosphatase values which are so disturbing?

Dr. Andrew Mitchell, assistant clinical professor of surgery (urology): The acid phosphatase, I presume, is reported in millimoles, which means that it's double the normal value and would be considered pathognomonic of carcinoma of the prostate. I think the occurrence of carcinoma of the prostate in a man 72 years old would be frequent enough that the likelihood of his having two diseases would be greater than the likelihood of the carcinoma of the prostate explaining all the present picture. I would say that his renal manifestations were on a basis of preexisting renal damage which probably antedated his resection. He had gone beyond a point where he would recover simply from having the obstruction removed. He probably had two diseases. This terminus for carcinoma of the prostate would be much rarer than the coincidental finding of carcinoma of the prostate. Probably from 20 to 30 per cent of all 72-year-olds have carcinoma of the prostate.

Dr. Delp: You wouldn't be disturbed by the absence of any bony lesions appearing in the x-ray films?

Dr. Mitchell: No, I wouldn't because he could have had enough lymphatic metastases to explain that elevation of acid phosphatase. He wouldn't have had to have bony lesions. Of course that's not much

of a KUB x-ray to rule bony lesions in or out on, but I don't think the whole thing can be explained on that basis. As far as his shock was concerned, one morbid finding of the carcinoma of the prostate and one not too greatly publicized is involvement of the adrenals. A good many people terminate their carcinoma of the prostate from adrenal failure with replacement by carcinoma of the prostate.

Dr. Delp: Now I'm just a little disturbed about the trend the clinical discussion has taken here. Dr. Rankin, I want to ask you your opinion concerning the possibility of intrahepatic metastatic lesions producing a blood cholesterol of 900 and an alkaline phosphatase of 50.

Dr. Thomas J. Rankin, assistant professor of medicine: As far as experience is concerned in the literature, it is very uncommon for alkaline phosphatase and cholesterol, both of which are phenomena seen in biliary obstruction, to rise to these levels from intrahepatic disease. The question has been asked heretofore by Dr. Delp if this might be a homologous serum jaundice. In common with all the rest of us I cannot in any terminal disease of the liver of this degree make that differential diagnosis. I am much inclined to feel that the thing is extrahepatic biliary obstruction because of the extreme level of the total cholesterol, because of the extreme level of the jaundice, and because of the extreme level of the alkaline phosphatase. As far as the clinical picture is concerned, I would certainly feel it to be clinically rather typical of so-called hepatorenal syndrome.

I cannot, of course, state how much of renal disease was due to chronic pyelonephritis which a man of this age with benign prostatic hypertrophy must have, but I think that the rapidly rising NPN and the terminal picture do certainly suggest the so-called hepatorenal syndrome. Since the man passed from 1000 to 1500 cc. of urine, I think that acute renal failure is less likely than the so-called bile nephrosis.

I believe then he had two causes for his renal failure: the original chronic pyelonephritis and the superimposed renal damage which accompanied his hepatic disease. I think time is too short to discuss the causes of death in hepatic coma and in azotemia. They are very confused and nobody can select the actual metabolic reason. I do certainly think that they do play primarily upon the central nervous system and the basal ganglia as one of the mechanisms of death.

Dr. Delp: May we hear from the pathologist, Dr. Joffe.

PATHOLOGY REPORT

Dr. Irwin Joffe, resident in pathology: There was a tumor which diffusely infiltrated the head of the pancreas and also involved the terminal one and one-half centimeters of the common bile duct. The tumor also involved the mucosa of the duodenum in the vicinity of the ampulla of Vater, involving just a small area about one centimeter square. The lesion in the head of the pancreas was poorly delimited and was a greenish-yellow in color. It appeared to involve grossly the root of the mesentery. The tumor involving the distal end of the common bile duct, which incidentally was not completely occluded, involved the mucosa and submucosa. In the area examined, it appeared not to penetrate the muscularis to involve deeper structures but some of this material, as you will see in the specimen, remains for your examination. It seemed likely to me that in some areas there was connection between the lesion in the distal common bile duct and the head of the pancreas. There was dilatation of the pancreatic duct, the duct of Wirsung, to a maximum circumference of three centimeters. The common bile duct was greatly dilated above the constricted lower portion to five centimeters in diameter. The cystic duct was two centimeters in greater circumference and the gallbladder was greatly enlarged, measuring 15 x 7 cm.

There were small masses of apparently thrombotic material partly occluding the superior mesenteric vein and the inferior vena cava in the vicinity of the pancreas. Another thrombotic mass was found in the right branch of the portal vein. Associated with this there were incomplete focal infarcts in the right lobe of the liver.

There was, of course, jaundice of all organs. The kidneys particularly were jaundiced and somewhat swollen. They weighed 420 grams together. The cortical medullar junctions were somewhat indistinct and the calyces on the left were slightly battered. The ureters were not dilated, the bladder was quite small and showed a mild acute cystitis. The prostate was small. It showed no evidence of recent operation and no evidence of nodular hyperplasia of any significance and no carcinoma grossly.

Dr. Harry S. N. Greene, professor of pathology at Yale: Several years ago following statements that autopsy was a much overrated pastime, my staff suggested that I was a disturbing influence at clinicopathological conferences and it might be well if I stayed away. This sort of thing is getting to be an unusual experience with me.

Morphologically in this case, interest centers around a tumor in the head of the pancreas. The question of interest from the pathological or academic point of view is the location of the point of origin. Is it in the head of the pancreas, pancreatic duct or in the common bile duct? I think that usually can be fairly well guessed at from the morphology.

There are two types of tumor structure. One area shows a rather anaplastic tumor. Quite obviously it is an adenocarcinoma but quite disorganized and undifferentiated.

Other areas show a good deal more organization

and definite acinar-like structures, an adenocarcinoma without question. Well, that doesn't help any, that may come from any one of those places. The head of the pancreas itself was a seat of a widespread chronic fibrosis, with not much indication of an origin. However, it could be the head of the pancreas. The pancreatic ducts were very interesting.

Frequently one found inside the ducts areas of polypoid hyperplasia which superficially and under low power looked something like cancer. However, they're not cancer. These were well differentiated cells and it was simply the hyperplasia appearing in those ducts following obstruction.

The epithelial surface was absent but in its wall were found structures which duplicated very well the acinar structures found in the tumor. However, whether this was invasion of the wall of the common bile duct from outside or from epithelia that desquamated simply can't be told. Thus, we're left in the dark as to the origin of this tumor, whether it was from the head of the pancreas or from the common bile duct.

A very interesting feature of this tumor was its widespread extension along lymphatics, particularly along perineural lymphatics.

There were thrombi in various regions in the inferior vena cava and periportal veins and inside of these thrombi there were growing cancer cells and also cancer cells in the walls of the vein. There were one or two minute lesions in the liver which could be construed as metastases. There were, however, no metastases elsewhere in the body.

The liver showed, as might be expected, evidences of an obstructive jaundice, some fibrosis and bile products.

Cholemic nephrosis of the kidney, degeneration of the epithelium and proximal tubules, and bile stained casts appeared in those slides.

There were masses of growing bacteria in the pneumonia of the lung.

So, from a biological point of view, interest in this case is in the fact that there were so few metastases. There was widespread extension of the tumor in lymphatics but metastasis was limited to two or three questionable lesions in the liver.

There is a tremendous difference between lymphatic extension and metastasis. Every time a cell undergoes mitosis the pressure inside the mass increases. The growing cells therefore take the path of least resistance in their continued extension. If there happens to be an open tissue space or a lymphatic, it will proceed to the regional lymph node where it will expand into a large mass. Tumors can extend for tremendous distances along lymphatics. I recall a case, for example, that showed extension of a breast carcinoma all the way down to a popliteal lymph node by means of lymphatic extension.

Metastasis is an entirely different circumstance. It's a discontinuous growth. It requires the tumor's having undergone a much longer development. It not only is capable of extension, it is capable of true invasion. There is a difference between extension and invasion.

One case of mine showed extension of tumor along tissue spaces between muscle fibers. If the muscle fiber is caught between two expanding masses it undergoes pressure atrophy and the tumor grows into that area. That is simple tissue occupation, the way a basal cell tumor grows.

True invasion is somewhat different and it's important to distinguish between invasion and extension for, as far as I am aware, the appearance of true cellular invasion is the only morphological criterion of metastasizing ability in the tumor. Unfortunately it can't be found in all situations for in order to find it, the cells adjacent to the tumor must be bigger than the tumor cells themselves.

Invasion is one of the necessities of metastasis. The tumor cell, in order to metastasize, must possess the ability to invade vascular walls. Once it gets inside a blood vessel it must possess the ability to survive living in the normal blood stream of the individual. In addition, after it has lodged in some endothelial surface, it must have the ability to invoke a stroma locally and then to grow extravascularly.

Well, how about this case, what was missing? Was the tumor autonomous? We don't know because no test for autonomy was made. Tumors of the common bile duct do become autonomous and do metastasize.

We know that tumor cells were present in the blood stream because we found them in growing thrombi. Why then, weren't there more metastases? Perhaps it's concerned with the inability of the tumor cells that were circulating in the blood stream of this individual to obtain a stroma. And stromatization of circulating tumor cells is extraordinarily important in the formation of metastases. Stromatization of circulating tumor cells is determined by exactly the same factors that govern stromatization of the graft.

Stromatization of tumor or graft cells depends on two factors: first, the ability of the cells to invoke a stroma, and second, the responsiveness of the connective tissue at the transplantation site. Both of those factors vary a great deal.

The ability to invoke stroma varies enormously. Some parenchymatous cells, for example those of the kidney or of the breast, are good stroma inducers. Other cells, such as those of the adrenal or the brain, are tremendously poor stroma inducers. As a matter of fact, ability to induce stroma seems to be directly proportional to the amount of connective tissue required by the parenchymous cells to form an adult structure. The kidney and the breast are complicated

admixtures of stroma and parenchyma and their cells are good stroma inducers. On the contrary the brain and the adrenal have a very small stromal content and in turn are poor stroma inducers.

The ability of connective tissues at various sites also differs widely in its ability to respond to a stroma inducing stimulant. If, for example, one takes a poor stroma inducer such as the embryonic adrenal and puts it into the subcutaneous space of an animal, it obtains no stroma whatsoever. The poor stroma inducing capacity of that adrenal is not sufficient to invoke a stroma from the very insensitive connective tissue of a subcutaneous space. Perhaps the most insensitive connective tissue in the whole body is that of the subcutaneous space and that is one of the reasons why skin transplantation is so difficult. However, if the embryonic adrenal is transferred to the anterior chamber of the eye, the poor stroma inducing stimuli are sufficient to invoke a stroma from this very responsive connective tissue in the iris.

Occasionally one finds tumors that have extraordinarily poor stroma inducing capacities. An outstanding example is the hypernephroma of the kidney. Such a kidney may grow to enormous size in an individual, actually become autonomous, invade the renal vein and at the time of operation it's obvious that there must be tumor cells in the blood stream. Yet after operation, such a patient may do perfectly well and never show metastases. And that is due to the fact that the cells of a hypernephroma are such poor stroma inducers.

If one transplants, for example, an autonomous hypernephroma from a human being into a guinea pig's eye, the cells grow but they grow in a manner of tissue culture, imbibing nutrient from the surrounding aqueous tumor. However, if such as tumor is transplanted to the brain, the extraordinarily responsive connective tissue of the brain will respond to this stimulus and a stroma will form.

The situation of the brain is extremely interesting in passing. Here one has a parenchyma which is probably the poorest stroma inducer there is, but a connective tissue which is the most responsive. If the situation were different and if in the brain we had a parenchyma that was a good stroma inducer, we'd undoubtedly have many more fibrous brains and a great deal more trouble getting along with clinicians. As a matter of fact, that is the reason why the brain tumors, the glioblastoma multiforme and the medulloblastoma, never metastasize. The tumor cells do get into the blood stream but they are such poor stroma inducers that they will not induce a stroma in any connective tissue in the body other than that of the iris and the brain.

Let me mention how some of these tumors can be transplanted, a tumor of a very poor stroma inducing capacity such as the hypernephroma. We can transplant them by means of a middle man and this technique illustrates very well, I think, the two factors concerned in transplantation and metastases: stroma inducing abilities and connective tissue responsiveness. We've been able to transplant such poor stroma inducers as hypernephroma to the anterior chamber of the eye by using the middle man. Embryonic tissue contains a very responsive connective tissue and it's also a good stroma inducer. The technique therefore is then a double transplantation. We first transplant embryonic guinea pig lung to the anterior chamber of the eye. That tissue, being a good stroma inducer, induces stroma in the adult iris. Then later on, we transplant the hypernephroma to the embryonic transplant. The embryonic connective tissue in the lung, being such a good and responsive connective tissue, responds to this poor stroma inducing stimulus and gives it a stroma.

The question remains why there were so few metastases in this individual? It would appear that the tumor was autonomous. It got into the blood stream and undoubtedly survived circulation in the blood stream. Now, not all autonomous tumors have that capacity. Not infrequently an animal tumor, one that is metastasized in the susceptible host, if removed and ground into emulsion and injected into the blood stream of a normal animal produces nothing whatsoever. The tumor cells are killed by the normal blood stream. It has been presupposed in many cases that some alteration must exist in the blood stream of a patient with metastatic tumor to allow metastasis to occur.

The other possibility in this case is that the tumor cells circulated but did not become stromatized. This is an adenocarcinoma and should be a good stroma inducer. But perhaps something happened to the connective tissue in this individual which made it unresponsive. I've no answer to this whatsoever but it is a fact, I believe, that in patients with arteriosclerosis, metastases are comparatively rare. They do occur but never in the abundance that they do in normal individuals.

ANATOMICAL DIAGNOSIS

Primary

Adenocarcinoma of the common bile duct with extension into the root of the mesentery, the descending portion of the duodenum, the head of the pancreas, the liver, celiac and peripancreatic lymph nodes and sympathetic nerves and ganglia.

Dilatation and polypoid hyperplasia of the duct of Wirsung and dilatation of the major extra and intrahepatic bile ducts, advanced with bile stasis.

Atrophy of parenchyma of the pancreas, advanced (history of fasting blood sugar 132 mg. per 100 cc.).

Organizing thrombosis of the portal veins and inferior vena cava containing proliferating tumor cells

Dramamine's® Effect in Vertigo

Dramamine has become accepted in the control of a variety of clinical conditions characterized by vertigo and is recognized as a standard for the management of motion sickness.

Vertigo, according to Swartout, is primarily due* to a disturbance of those organs of the body that are responsible for body balance. When the posture of the head is changed, the gelatinous substance in the semi-circular canals begins to flow. This flow initiates neural impulses which are transmitted to the vestibular nuclei. From this point impulses are sent to different parts of the body to cause the symptom complex of vertigo.

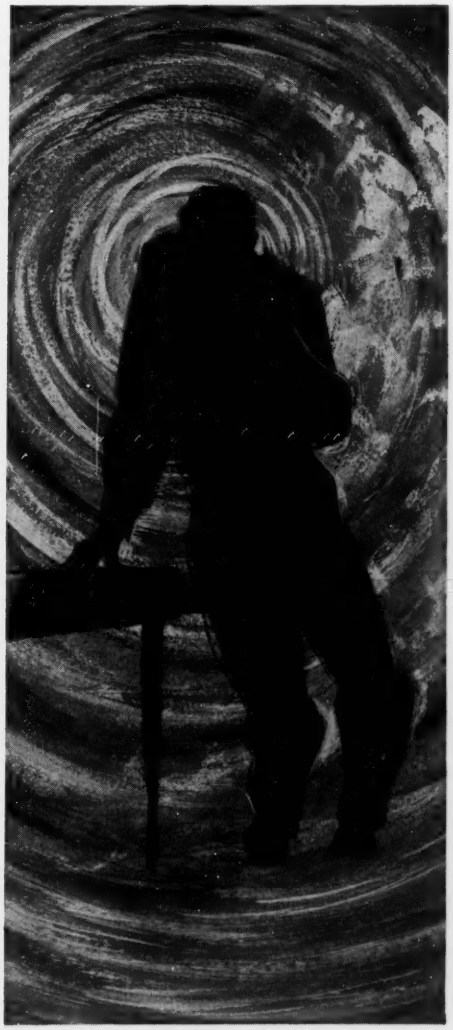
Some impulses reach the eye muscles and cause nystagmus; some reach the cerebellum and skeletal muscles and righting of the head results; others activate the emetic center to result in nausea, while still others reach the cerebrum making the person aware of his disturbed equilibrium. *Vertigo may be caused by a disease or abnormal stimuli of any of these tissues involved in the transmission of the vertigo impulse, including the cerebellum and the end organs.*

A possible explanation of Dramamine's action is that it depresses the overstimulated labyrinthine structure of the inner ear. Depression, therefore, takes place at the point at which these impulses, causing vertigo, nausea and similar disturbances, originate. Some investigators have suggested that Dramamine may have an additional sedative effect on the central nervous system.

Repeated clinical studies have established Dramamine as valuable in the control of the symptoms of Ménière's syndrome, the nausea and vomiting of pregnancy, radiation sickness, hypertension vertigo, the vertigo of fenestration procedures, labyrinthitis and vestibular dysfunction associated with antibiotic therapy, as well as in motion sickness.

Any of these conditions in which Dramamine is effective may be classed as "disease or abnormal stimuli"* of the tissues including the end organs (gastrointestinal tract, eyes) and their nerve pathways to the labyrinth.

Dramamine (brand of dimenhydrinate) is supplied in tablets of 50 mg. and liquid (12.5 mg. in each 4 cc.). It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. G. D. Searle & Co., Research in the Service of Medicine.



The site of Dramamine's action is probably in the labyrinthine structure.

*Swartout, R., III, and Gunther, K.: "Dizziness:" Vertigo and Syncope, GP *8*:35 (Nov.) 1953.

and organizing thrombosis of the superior mesenteric vein.

Focal incomplete infarcts of the right lobe of the liver.

Pericholangiohepatitis, slight.

Generalized jaundice, advanced.

Cholemic nephrosis, advanced.

Focal hemorrhages in the gums, submucosa of the small and large intestine, adventitia of the root of the aorta, beneath the pleurae of the lower lobes of both lungs, and in the skin (history of prothrombin time of 25 per cent of normal).

Emaciation.

Acute focal esophagitis (history of gastric intubation, 1 day).

Traces of gastric contents and mucus in trachea (history of coma, 3 days).

Bronchopneumonia of all lobes of both lungs, advanced, weight 2570 grams, with aspiration bronchopneumonia in upper lobe of left lung.

Dilatation of the heart, slight.

Acute passive congestion of the liver and spleen, moderate.

Ascites, 100 ml.

Acute cystitis, slight (history of indwelling catheter, 3 days).

Accessory

Arteriosclerosis of the left anterior descending coronary, basilar and left vertebral arteries, advanced; of the left circumflex and right coronary arteries, aorta, both middle cerebral and right vertebral arteries, moderate; of the anterior cerebral arteries, slight.

Sclerosis of the anterior leaflet of the mitral valve, slight.

Healed intramural anteroseptal myocardial infarct, small.

Interadherence of the cusps of the aortic valve, slight.

Fibrous thickening of the appositional surfaces of the mitral valve, slight.

Calcified lymph node at the hilum of the right lung.

Fibrous pleural scar of the apex of the upper lobe of the right lung.

Fibrous pleural adhesion between upper and lower lobes of the left lung.

Emphysema of the anterior borders of both lungs, moderate.

Arterial and arteriolar nephrosclerosis, moderate.

Chronic pyelonephritis, left, slight.

Retention cysts of the left kidney, slight.

Multiple diverticula of the colon.

Acute ulcerative proctitis, moderate.

Pedunculated polyp of the sigmoid colon.

Adrenal rest in region of celiac ganglion.

Accessory spleen.

Partially edentulous mouth.

Arcus senilis.

ACTIVITIES OF MEMBERS

Dr. and Mrs. D. V. Conwell, Wichita, are touring the continent of Europe following Doctor Conwell's presentation of a paper at a medical meeting in London, England.

Upon completion of a surgical residency in Research Hospital, Kansas City, Missouri, Dr. James D. Colt V, has resumed his association with his father, Dr. J. D. Colt, Jr., in Manhattan.

Dr. Marita Scimeca has recently begun practice in Kiowa, Kansas. Since her graduation in 1951, Doctor Scimeca has been practicing with her father in his office in Iola.

Some 350 persons joined a community party honoring Dr. C. E. Burtch of Portis, Kansas, as he completed his fiftieth year of practice in the medical profession.

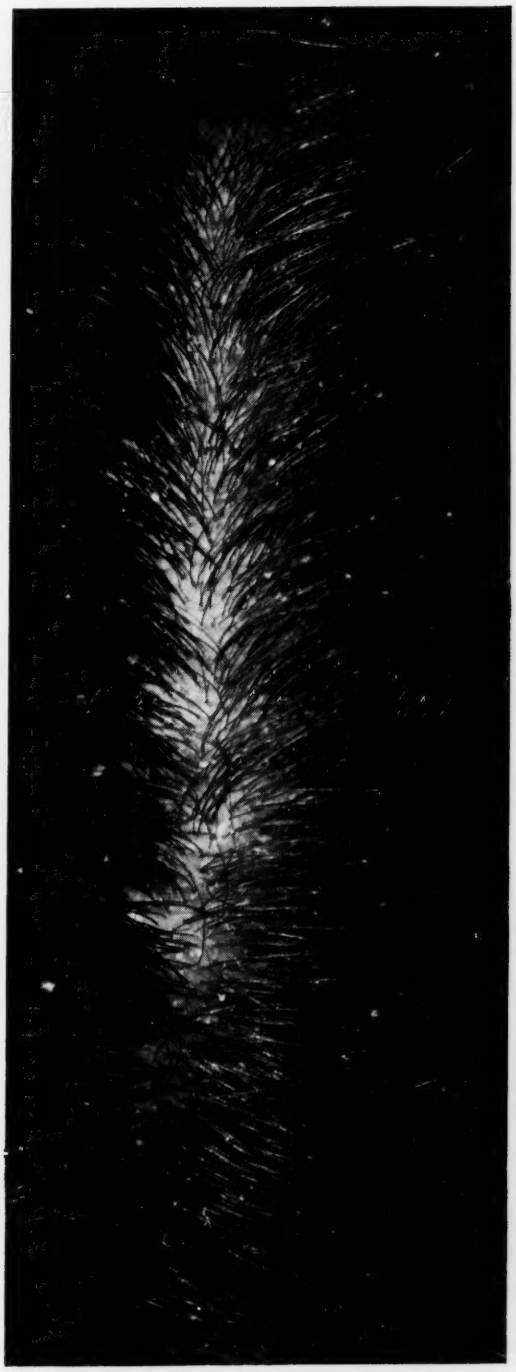
Doctors V. E. Chesky, William C. Dreese, and C. A. Hellwig of Halstead presented a scientific exhibit on "Colloidophagy in the Thyroid Gland" during the June meeting of the American Medical Association in San Francisco.

Dr. C. T. McCoy has recently opened an office in Hutchinson.

At the recent meeting of the American Medical Association in San Francisco, Dr. Charles Pokorny of Halstead read a paper on "Diffuse Interstitial Fibrosis of the Lungs."

Dr. Carter B. Sigel has recently reported for duty in the U. S. Navy at the Naval Hospital, Oakland, California.

A brief note from Dr. Mary Glassen of Phillipsburg arrived from Geneva, Switzerland, where she attended the International Congress of Gynecology and Obstetrics, July 26-31. She says, "It is a brand-new experience for me to use the earphones constantly for interpretation of the four languages officially used. Naturally, I'm unreasonably proud of the U. S. participants. . . ." She also attended a meeting of the World Health Organization and closes



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by saying that Europe has been wonderfully cool with Geneva almost too cool for comfort.

Dr. R. G. Rate, formerly of Veteran's Administration Hospital in Kansas City, has joined the staff at Hertzler Clinic in Halstead as head of the Department of Thoracic Surgery.

Dr. William J. Smith and family left for Warrensburg, Missouri, where his family will remain during Doctor Smith's tour of duty in the U. S. Navy.

Dr. Arthur L. Duell who was previously associated with the Gelvin-Haughey Clinic at Concordia, has recently opened an office in Clifton, Kansas.

Dr. Karl Menninger and five staff members of the Menninger Foundation have recently completed participation in a series of International Meetings on Mental Health in Toronto, Canada.

Dr. J. G. Claypool who recently left Howard, Kansas, to complete a residency in Internal Medicine, presented an exhibit at the June meeting of the American Medical Association in San Francisco.

Dr. Edward M. Burrell, began his medical practice in Turon, Kansas, on August 1, 1954.

Dr. Ernest P. Carreau has recently been released from active duty with the U. S. Navy and has recently made his residence at 461 South Glendale Street, Wichita, Kansas.

Dr. Porter E. Barbera has reported to the Brook Army Medical Center at Fort Sam Houston, Texas, to begin a two-year tour of duty in the U. S. Army.

Dr. Edward Maier has left Arkansas City for Rochester, Minnesota, where he has accepted a three-year fellowship with the Mayo Clinic.

ANNOUNCEMENTS

The Omaha Mid-West Clinical Society will hold its 22nd Annual Clinical Assembly, October 25-28, at the Hotel Paxton, Omaha, Nebraska.

The program includes guest and member speakers who will present addresses, clinics, panel discussions, question and answer periods, as well as other interesting features.

For further information, write the executive office of the Society, 1031 Medical Arts Building, Omaha, Nebraska.

Heart Meeting Canceled

Dr. P. W. Morgan, Chairman of the Committee on the Study of Heart Disease, announced that the 1954 annual postgraduate course in cardiology which was to be held at Emporia, Kansas, in October has been canceled. Plans for the 1955 meeting are now in progress.

The Kansas Medical Society Annual Meeting

The annual meeting of The Kansas Medical Society will be held at Hutchinson, Kansas, May 1-5, 1955.

Clinical Session of the A.M.A.

The mid-winter meeting of the American Medical Association will be held at Miami, Florida, November 29 through December 3, 1954.

Annual Meeting of the A.M.A.

The annual meeting of the American Medical Association will be held in Atlantic City, N. J., June 6-10, 1955.

40th Annual Clinical Congress of the American College of Surgeons

The 40th annual Clinical Congress of the American College of Surgeons will be held in Atlantic City, N. J., November 15-19, 1954.

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The Kansas State Board of Medical Registration and Examination at its regular session passed a resolution on June 9, 1954 stating that National Board Certificates issued on the basis of examinations, as presently conducted, would no longer be recognized as endorsement for licensure in this state.

COUNTY SOCIETIES

The Sedgwick County Medical Society has completed the construction of an executive office building and is now housed in new quarters at 1102 South Hillside, Wichita, Kansas. The telephone number also has changed to 63-7557.

This beautiful structure not only houses the executive office in air conditioned comfort, but contains their medical library and an attractive auditorium which is to be used for society and for public meetings of interest to medicine. Congratulations to the progressive society for another project successfully concluded.

BLUE SHIELD

The Doctor's Voice in Blue Shield

Comments received from physicians during the recent charge survey prompt us to again point out the doctor's voice in his "Health Plan," Blue Shield.

The Blue Shield Plan which Kansas doctors are concerned with, does and must have the approval of the Kansas Medical Society. The president and president-elect of the Society, along with a member from each Medical Councilor District, are on the Blue Shield Board. With the exception of three lay persons, the Board is composed entirely of Doctors of Medicine.

The Blue Shield Board of Trustees has supervision and control of the business, property, affairs and management of the corporation.

In addition to having control of the Board, the Kansas Medical Society appoints and controls two committees whose functions are of prime importance to Blue Shield operations. They are the Blue Shield Fee Committee and the Blue Shield Relations Committee.

The Blue Shield Fee Committee is composed of a representative from each of the medical specialities. It is the duty of this committee to accumulate and evaluate all suggestions and complaints from Participating Physicians and to then make recommendations to the Board for changes or additions to the Blue Shield Schedule of Allowances.

Any time a doctor participating in Blue Shield is dissatisfied with the Schedule of Allowances, he should make his feelings known to his representative on the Fee Committee.

Each of the Medical Councilor Districts provides a representative to make up the Blue Shield Relations Committee. These Councilor District representatives become chairmen of the District Relations Committees and each appoints a member from his County Society to round out his committee.

A staff member from Blue Shield meets with these District Relations Committees once or twice each year to discuss matters of policy, financial condition or any anticipated changes in the program. Through this means, each County Society's views are made known.

At this point, there should be little doubt as to the doctor's voice and the channels through which it can be expressed. If the individual doctor feels he has been by-passed in the process of policy making, perhaps it is because he hasn't made his wants known through the proper committee, or has assumed the attitude that his views are unimportant.

With the interested participation of all Society members, Blue Shield will prosper and remain truly the "Doctor's Health Plan."

Annual Fall Conference
Kansas City Southwest Clinical Society

The 32nd Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society will be held in the Municipal Auditorium, Kansas City, Missouri, October 4, 5, 6, 7, 1954.

In addition to scientific lectures by the sixteen distinguished guest speakers, they will take part in seminars, conferences, and panel discussions, as well as the daily round table luncheon question periods.

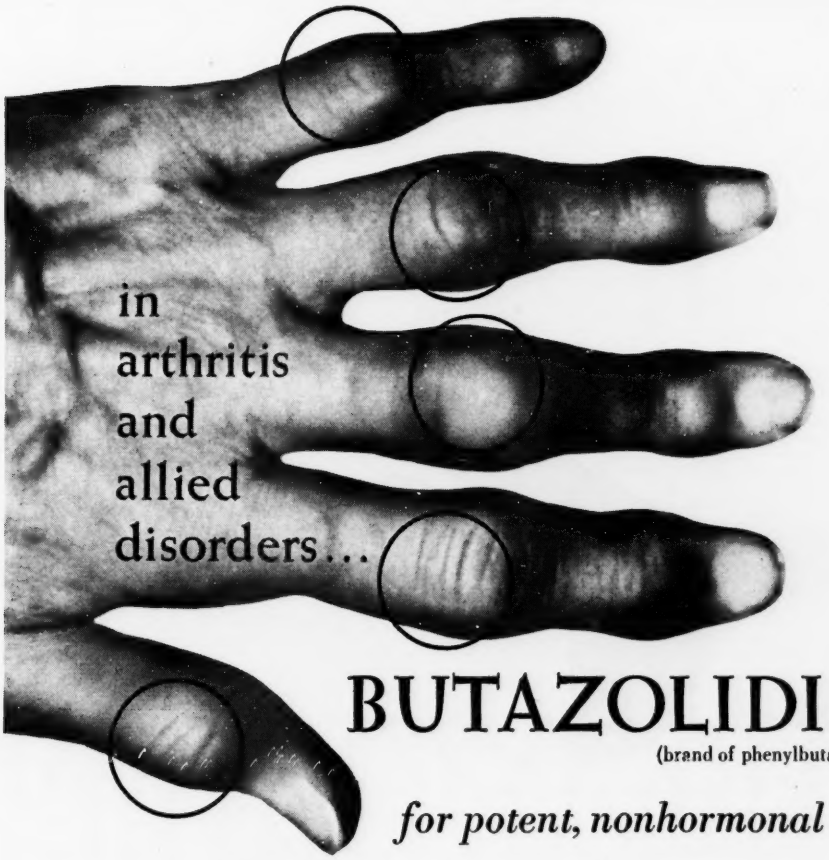
The colored television program will be presented on the mornings of October 5, 6, and 7; many with guest speaker participants. This feature of the conference will include Operative Clinics, Clinical Demonstrations, and How You Do Its.

Your September-October copy of the *Kansas City Medical Journal* will reach your desk about the middle of September. Refer to it for the complete program of the Conference and plan to attend.

NOTICE

Members having material of historical interest relative to medicine or physicians of Kansas, please send it to the:

Committee on History
The Kansas Medical Society
315 West Fourth Street
Topeka, Kansas



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*MacKnight, J. C.; Irby, R., and Toone, E. C., Jr.: Geriatrics 9:111 (Mar.) 1954.

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Adverse Effects of Penicillin Therapy

W. D. Bradshaw, M.D.*

Penicillin entered the armamentarium of the medical profession with dramatic and startling effectiveness in the early 1940's marking the beginning of what has been termed the "Era of Antibiotics." Many other antibiotics have been developed and are in wide use today; however, penicillin continues to be the most widely used chemotherapeutic agent. Why has penicillin gained such widespread usage? Perhaps the answer to this question is to be found in the following thoughts: (1) penicillin is truly a wonder drug having real chemotherapeutic value; (2) the enthusiasm and insistence of the general public for penicillin therapy; and (3) the "memory" of the medical profession of the pre-antibiotic era when infections which seem insignificant now were often overwhelming and fatal.

One of the first reports of the clinical use of penicillin, published in March of 1943 by the Floreys,[1] made no mention of undesirable effects. In August of 1943[2] reports of untoward reactions began to appear in medical literature. During the past eleven years a voluminous amount of material has been published concerning adverse effects of penicillin therapy.

It is of importance to attain a workable knowledge of these adverse effects in order to realize the fullest therapeutic value of this agent. A clinical evaluation of penicillin is still far from complete, but some perspective concerning its present status is possible and in order at this time. The adverse effects produced by penicillin may be grouped and will be discussed as (1) hypersensitivity reactions, (2) effects related to bacterial alterations, (3) direct toxic reactions, and (4) effects on patient care.

EFFECTS RELATED TO HYPERSENSITIVITY TO PENICILLIN

Hypersensitivity or allergy to penicillin has received wide publicity in the past decade. Despite the fact that many competent people have and are investigating this problem, there remains much to be desired for adequate understanding. It must be remembered that our commercial penicillins are derived from a common mold which is known to be antigenic and which is widely distributed in nature.

Incidence: The incidence of penicillin allergy in the general population is extremely difficult to evaluate. Rhodes[3] reports an incidence of three to four per cent; Long,[4] an incidence of five per cent. It will be noted that the incidence of some small group or particular type of reaction reported in this paper will exceed the incidence which Long reports; a fact which illustrates the varying opinions expressed in the current literature as to incidence of these manifestations. It is interesting to note that most of the allergic manifestations reported in the literature have been in the adult population. Apparently these reactions are not common in pediatrics although such occur in children.

Immunology: Little is known concerning the basic immunology of the reactions. Most of the ordinary rules that one might expect to apply seem to be remarkably unreliable in relation to penicillin reactions. Penicillin combines with human serum albumin as shown by dialysis experiments; it is believed to possess antibiotic activity when in such combinations.[5] This fact might tend to make one think of penicillin as a haptene; however, such has not been proven.

Route of administration: The route of administration of penicillin is of consequence in the consideration of various hypersensitivity phenomena.

Topical application is commonly recognized today as a cause of contact dermatitis.[6] Sensitization is usually developed in the course of one to two weeks after the first contact with penicillin ointment. Allergic reactions have been reported from medical personnel handling penicillin.[7, 8, 9] Templeton, et al., in 1947,[10] reviewed the toxic reactions occurring after the topical application of penicillin solutions and ointments. They recommend that topical use be avoided; this recommendation has apparently been well accepted by the medical profession.

Local applications of penicillin in the form of lozenges and drops may cause local reactions such as apthous stomatitis, rhinitis, glossitis, and melanoglossia.[11, 12] The reaction may not necessarily be local, but may, in a highly sensitive individual, produce a generalized sensitivity reaction, even when penicillin is used in oral lozenge form.[13] Mayer, et al.[14] states that the incorporation of penicillin in gums, gargles, and mouth and throat lozenges should be condemned. Because of the increased potential of sensitization this mode of administration should be avoided and systemic medication substituted for greater efficacy.

Intrathecal administration of penicillin is not dangerous because of the sensitivity factors but rather as a direct toxin to the central nervous system. Attention

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* This is one of the theses written by fourth year students in the University of Kansas School of Medicine selected for publication by the Editorial Board from a group judged by the faculty at the school to be the best.

Thesis written while the author was a fourth year student. Dr. Bradshaw is now interning at the University of Kansas Medical Center, Kansas City, Kansas.

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will be given to this route of administration of penicillin as a direct toxic agent.

Keefer[15] states that the greatest incidence of sensitization arises from topical administration and the least from the oral route. Finland[16] states that although oral penicillin is only about 10 to 30 per cent as effective as intramuscular administration it has a relatively low sensitizing effect and can be used in sensitive individuals. He also states that the soluble forms have much less sensitizing potential than do the repository forms.

Types of penicillin: The large scale production of hypoallergic penicillins bears witness to the fact that penicillin reactions are attaining an incidence higher than the public or the medical profession will tolerate without comment. To understand the various types of penicillin, a brief statement in regard to the preparation of these compounds seems pertinent.

Penicillin is a generic term and designates a group of compounds that contain an alanine dimethyl cysteine nucleus but which differ in the side chain composition. A variety of "substituted penicillins" or "biosynthetic penicillins" can be prepared by incorporating the appropriate precursors in the media in which Penicillium Notatum is grown.[17]

Penicillin "G," characterized by a benzyl group in the side chain, is the most widely used commercial penicillin. Penicillin "O" or "AT" has a straight chain replacing the benzyl ring of penicillin "G"; its chemical term is allylmercaptomethyl penicillin. Penicillin "BT" also has a straight side chain; chemically termed N-butylthionethyl penicillin. "Compenamine" is 1-ephenamine penicillin "G." The claim of lesser potential of sensitization has been made for this preparation as has been made for penicillin "O" and "BT."

It has been demonstrated that there is considerable cross-sensitization between penicillin "G," "O," and "BT."[17] However, not all individuals show sensitivity to all such perparations; therefore, the usefulness of the different forms of penicillin should not be overlooked, since it might be possible to substitute the various forms if so required. Compenamine deserves further investigation before a true evaluation may be discussed.

Although chemical precursors may be fed to microorganisms producing penicillin in an attempt to produce a drug that is not normally produced or to overcome the sensitization problem, nature cannot be made to forget completely her natural manufacturing methods. Hence, according to the current information, penicillins BT and O probably contain a small amount of penicillin G as a contaminant. In general, the hypoallergic penicillins have not proven to be as useful as was anticipated.

Penicillin preparations combined with antihistamics have been used; this attempt to reduce hypersensitivity phenomena appears to have some merit. More study is needed for complete evaluation of this method of therapy.

A constant effort has been made since penicillin first became available to alter the molecule in such a manner as to enhance certain valuable properties. What effect do these additions to the penicillin molecule have on hypersensitivity phenomena? Penicillin in beeswax and oil produced an unusual incidence of the urticarial type of reaction especially at the site of injection. The oil and wax probably act as adjuvants increasing the tendency to sensitization in addition to delaying the absorption of antigens, thus producing a more severe local reaction.[19] There has been no conclusive proof that procaine has occasioned any additional sensitization, although it should be noted that sensitivity to procaine itself is a real possibility. Penethamate ("Neo-penil") has been shown to diffuse more readily into lymph glands, the respiratory tract, and central nervous system than penicillin G. However, serious side effects have been reported recently, rendering this product of questionable usefulness. Benzethasil ("Bicillin" or "Permapen") represents a modification of penicillin designed to produce prolonged plasma concentrations. There is no evidence incriminating this preparation as being more sensitizing than any other preparation. All of the preparations of penicillin representing chemical unions of two or more drugs must be evaluated carefully because the potentials of sensitization may be increased over the potential of penicillin alone.[20]

Biologic tests for hypersensitivity: Attempts to determine hypersensitive individuals by various biological tests are of interest. Procedures which are most frequently used in clinical medicine include the scratch, intracutaneous, patch, and inhalation tests.

The skin tests are conducted in the manner of the usual routine testing for hypersensitivities. The clinical significance is, as yet, open to some question; however, the tests do serve to call attention to possible disastrous effects that may follow penicillin administration. The following facts appear to be apropos:

1. Negative skin test does not rule out the possibility of a serious reaction.

2. A positive test in an individual with a history of previous penicillin reactions or a history of having had one or more courses of penicillin is certainly indicative of clinical sensitivity and the likelihood of a serious reaction should be considered.

3. Patients showing a delayed positive type of reaction to skin tests are probably not as likely to have immediate reactions as the more common urticarial or "serum-sickness" type of reaction.

4. A strong, immediate urticarial reaction to skin tests indicates a very unusual degree of sensitivity

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and the greatest possible danger if ordinary doses of penicillin are given.

5. The relative merits of the patch, intracutaneous, and scratch tests is much debated. It appears that the patch test is of questionable value.[21] Severe hypersensitive generalized reactions have occurred following intracutaneous tests.[22] Patients suspected of having a high degree of sensitivity should be tested first by the scratch method and then, if negative, by the intracutaneous method.

Inhalation tests using penicillin as an aeosol have been used to determine the reactivity of the bronchial tree or lung. Measurements of vital capacity are recorded as the allergen is inhaled.[23] This test has not been widely used and deserves more study for evaluation.

Several other biological tests are available but have not received as much clinical use as the skin tests. The methods that have been used are passive transfer or passive sensitization of human skin, the Dale reaction in guinea pigs, and precipitin tests for antibody production. These largely represent experimental studies designed to gain an insight into the basic immunology of these penicillin reactions.

Desensitization: Desensitization of individuals to penicillin has been attempted. Peck and Seigal[24] report a case of successful desensitization. However, such procedures have not been uniformly successful and deserve more study and evaluation.

Relation of penicillin to collagen diseases: Is there a correlation between penicillin hypersensitivity and the "collagen diseases"? Rich[25] showed a relationship of the hypersensitivity state to periarteritis nodosa, lupus erythematosis, serum-sickness, and rheumatic fever. A report by Walsh and Zimmerman[26] of six patients with penicillin reactions provides interesting speculation as to a relationship between lupus erythematosis and hypersensitivity. Three of their patients having severe penicillin reactions showed the "L.E." phenomenon and in the three with less severe reaction, the cells were not found. The authors draw no conclusions as to the role of penicillin in these cases. The question of a correlation between penicillin and the collagen diseases is indeed an interesting problem.

The commonly observed types of hypersensitivities to penicillin will be considered under the major groupings of dermatologic effects, serum-sickness-like reactions, immediate constitutional reactions, and other less common manifestations.

DERMATOLOGIC EFFECTS

The early reports of dermatological reactions were concerned only with urticaria, the incidence of which ranged between two to three per cent.[27] During the years of increasing penicillin usage, dermatological reactions have increased in variety and in frequency. Current literature includes epidermophytid-like lesions, dermatitis medicamentosa, contact dermatitis, the various urticarial groups, and many other dermatological descriptive lesions. In 1950, Long[4] estimated the incidence of dermatological reactions to be from 10 to 15 per cent, illustrating the greater frequency as more people are being exposed to penicillin. However, it must be realized that penicillin reactions are being recognized with greater frequency since more knowledge has accumulated concerning them.

A workable understanding of these reactions is probably best attained by a consideration of their pathogenesis and physical appearance. Reyer[29] organizes these reactions from the standpoint of their pathogenesis as follows:

Group A: Epidermal contact reactions with localized dermatitis and sensitization restricted to areas of application.

Group B: Dermal reactions regardless of the route of administration, whether by local application, by ingestion, by inhalation, or by injection.

Type I: Specific penicillin reactions.

Type II: Reactions to the vehicle, the base, or the culture medium upon which the penicillin is grown.

Type III: Nonspecific reactions to the common mold antigen.

Type IV: Jarish-Herxheimer reactions of the bacterial type from liberation of toxins from organisms killed by penicillin.

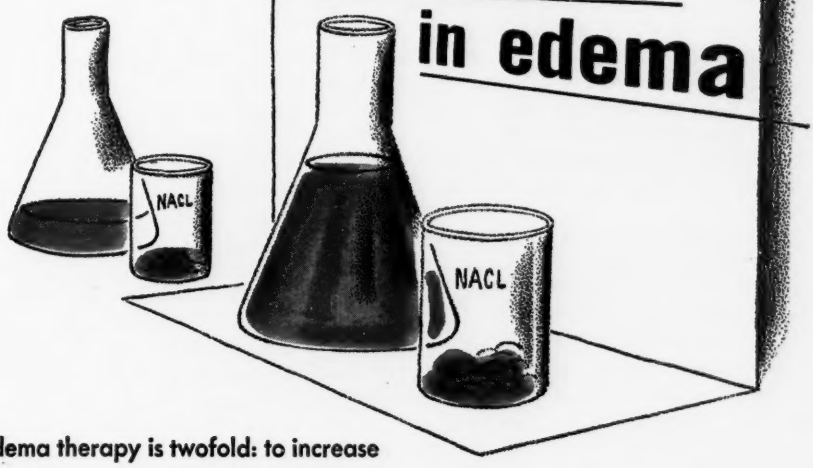
Type V: Reactions from a disturbance of the "symbiotic balance" of organisms growing on the skin surface.

A more complete view of the problem is gained by considering each of these mechanisms with the physical appearance and characteristics of the reactions.

Epidermal contact reactions: The epidermal contact reaction is a typical vesicular contact dermatitis. Sensitization usually develops in the course of one to two weeks after first contact with penicillin ointments. External contact may well cause a generalized dermal sensitization.[10] Because of the high index of sensitization as well as the possibility of inducing a generalized dermal sensitization, local use of this antibiotic has been condemned.

Dermal reactions specific to penicillin: Dermal reactions specific to penicillin consist primarily of the urticarial reactions. This reaction is a delayed type, coming on seven to twenty one days after the first administration of the drug and apparently is induced by treatment. This delayed incubation period may be shortened as an accelerated reaction seen in cases receiving a second or third exposure to penicillin. It appears to be a common belief that these urticarial reactions are easily controlled and may be of

increasing the excretion of water and sodium in edema



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1. Nielsen, A. L., Bechgaard, P., and Bang, H. O.: Low-Salt Diet in Treatment of Congestive Heart Failure. *Brit. Med. Jour.*, 1:1349, June 16, 1951.

2. Brown, W. E., and Sutherland, C. G.: Control of Edema in Pregnancy. *GP*, 8:65, Nov., 1953.

little consequence; however, Epstein[22] reports six patients in whom the urticaria persisted for from three to fifteen months. Each of the six patients remarked independently that he would rather have the infection for which the penicillin was given.

The urticarial type reaction of severe nature and associated with serum-sickness-like signs and symptoms will be discussed later.

Reactions to the vehicle: Many patients' case histories appearing in the literature do not mention testing for hypersensitivity to the vehicle, the base, the culture medium used to grow the penicillin, or to other brands of penicillin. It is, therefore, difficult to separate those reactions due to the penicillin itself from those due to the other agents. No characteristic physical appearance can be set forth for this group as the manifestations may vary with the responsible agent.

Non-specific reactions to the common mold antigen: This type of mechanism is probably responsible for most of the immediate eczematous, bullous, or vesicular eruptions often described. This type of reaction is frequently referred to as the "id" type of reaction because, at least superficially, it often resembles an attack of epidermophytosis involving particularly the interdigital spaces, the groin, and flexion creases. The characteristic time of occurrence is early with an incubation period of a few hours to not more than one day. Lesions are usually observed to be red, oozing, and itching. These reactions may also be of a severe nature; Huber[22] reported an exfoliative dermatitis following penicillin in a patient with a chronic epidermophyte infection about the feet of several years' duration. Twelve hours after injection of penicillin a generalized papulopustular eruption appeared, and on the sixth day the skin over the entire body exfoliated.

The Jarish-Herxheimer reactions: These dermal reactions are not due to penicillin sensitivity but are rather due to a sensitivity to the products of decomposition of bacteria or fungi. The bacteria or fungi that liberate the products must be nonresistant to penicillin, thus flooding the system with the toxins of the disintegrating organisms. This type of reaction is commonly observed to be of the eczematous type. Systemic reactions are of frequent occurrence in addition to the skin manifestations.

Symbiotic imbalance: The effect of penicillin in altering normal flora of the host is certainly a complex problem. Skin organisms of course share in this disturbance as do the micro-organisms in other parts of the body. Many cases listed as allergic eczematous eruptions, id eruptions, or flareups of fungal infections may ultimately be traced to such imbalances of skin organisms brought about by the sudden presence of penicillin. This interesting concept will be discussed further as "superinfections."

DELAYED "SERUM-SICKNESS-LIKE" TYPE OF REACTION

The term "serum-sickness" type of reaction appears to be a very applicable term because this type of reaction can imitate practically all of the usual features of a reaction to heterologous serum. This is probably the commonest type of hypersensitivity to penicillin. The incidence of these reactions as reported in the literature varies from one per cent[20] to six per cent[14] of all patients receiving penicillin.

Cecil[18] defines serum-sickness as "an allergic reaction resulting from the parenteral administration of a foreign serum and characterized by an incubation period, skin eruption, enlargement of lymph nodes, fever, edema, and polyarthritis."

Like serum-sickness this type of reaction has an incubation period of about five to fourteen days. This delayed reaction time and incubation period probably indicates that the patient is developing sensitivity as a result of administration of the drug.

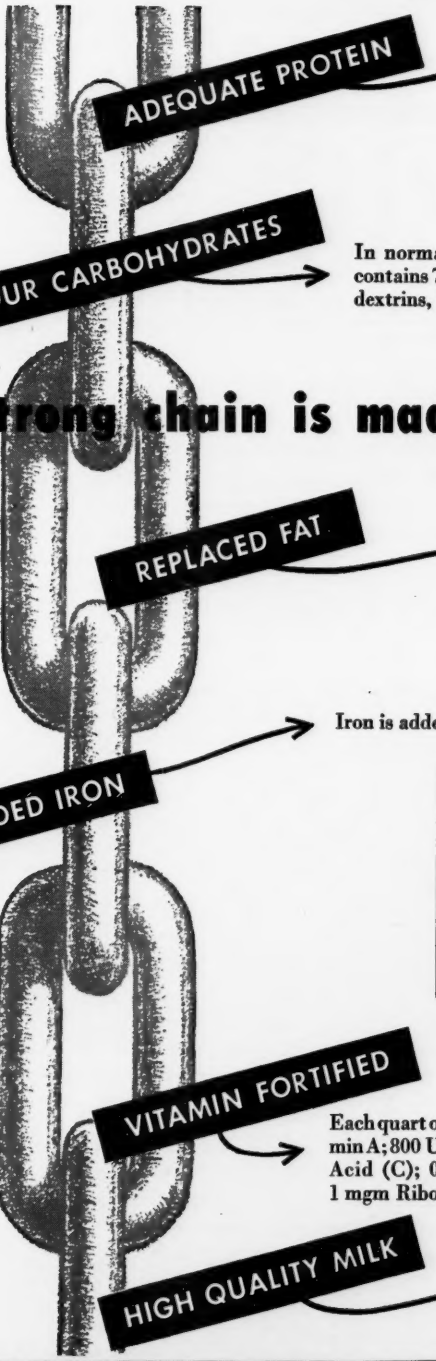
Intramuscular injections of the drug have been reported as the most frequent mode of administration although these reactions occasionally follow oral therapy. In many instances previous local applications have been the most likely cause of the hypersensitivity. Riley[28] reporting twenty-two cases of serum-sickness from penicillin states that eighteen of the twenty-two previously used penicillin locally.

The predominant feature is urticaria and angioneurotic edema. The palms of the hands and soles of the feet are characteristically involved with the urticaria. Severity of this reaction varies, as it does with serum-sickness, from a relatively mild and brief urticaria to an extremely severe illness which may last for several weeks. There is often an arthalgia and swelling of the joints, particularly the small joints of the hands and feet. Fever is a variable finding. It may be absent or negligible in mild cases or it may be as high as 105° in more severe cases. Patients presenting themselves complain bitterly of severe pruritis which usually begins just prior to the urticarial formation and may continue in the face of therapy.

Gastro-intestinal symptoms may or may not be associated with this reaction. The symptoms most often described are nausea and vomiting with accompanying anorexia. Diarrhea is infrequently a complaint.

Psychogenic symptoms are often marked. Apprehension of striking magnitude is frequently observed. Toxic psychosis appearing in a patient reported by Kline and Highsmith[30] was thought to be due to edematous lesions in the brain resulting from a localized penicillin hypersensitivity. However, the usual symptoms seen are those of severe apprehension often accompanied by moderate to severe malaise.

The duration of this reaction is extremely variable, ranging from four or five days to eight weeks or



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more. It is important that these patients be informed that the antigenic substance will, in time, be excreted or changed in such a manner that the reaction will subside.

SEVERE IMMEDIATE CONSTITUTIONAL REACTIONS

Although unfavorable reactions to penicillin therapy are well known, the occurrence and frequency of serious, life-threatening, immediate constitutional reactions have only recently been generally recognized. The incidence of these severe reactions is at best an approximation and probably is impossible to calculate because only a fraction of such reactions are publicized.[31] It seems that this problem is becoming a more frequent one. During the 15 month period preceding February, 1953, there were 15 cases of penicillin anaphylaxis published and, of these, six were fatal. By contrast from 1946 to 1951, there were only six cases reported with but one fatality.[20] It is almost universally accepted that the number of penicillin sensitive persons is increasing with widening use of this powerful drug. This statement or similar ones are repeatedly found throughout the current literature.

The immediate constitutional reactions to penicillin present a fairly characteristic picture. The onset is rapid, ranging from a few seconds to several minutes after administration of the drug. Complaints frequently offered by patients include: strange taste sensations, itching, a feeling of compression of the chest, feelings of impending death, difficult breathing, weakness and extreme nervousness. The most important objective signs are those of shock, with a profound fall in blood pressure, labored slow breathing, and cyanosis. Death occurs within the space of a few minutes to two or more hours and appears to result from shock or asphyxia.

Starling[32] sets forth five cardinal symptoms which serve as a forewarning of this type of reaction. These symptoms are: (1) syncope, mild to severe, at the time of injection, or a feeling of faintness recurring periodically for the following three to four hours; (2) sensation of burning or heat throughout the body, especially in the throat, palms of hands, or soles of the feet (similar to reaction following intravenous calcium); (3) local or generalized pruritis, never before present, may occur in various parts of the body, beginning within a few hours after injection; (4) choking sensation in the throat, with increasing cough, dyspnea, and wheezing; (5) severe paroxysmal pain varying in location, such as precordial, epigastric, or diaphragmatic.

There is no predictable pattern in penicillin hypersensitivity reactions; several courses of penicillin may not give rise to symptoms before and even after severe allergic reactions.[33]

The route of administration which has most commonly been reported in association with these severe reactions is intramuscular. It should be realized, however, that accidental intravenous injection may have been responsible for many such reported reactions. These hypersensitivity phenomena are not restricted to the intramuscular route; severe reactions have been described from intranasal instillation,[34] aerosol,[35] oral administration,[36] and intracutaneous skin tests.[37] Information at the present time does not incriminate any one single preparation of penicillin. It is possible that some of these reactions may be due to a hypersensitivity to procaine; however, one published fatality[38] can be blamed on the fact that the author reporting it was led to believe that a previous anaphylactic reaction in that patient was due to the procaine rather than the penicillin.

Pathological studies indicate that changes likely to be found are emphysema, edema in the lungs and bronchi, congestion of the lungs with small hemorrhages, and congestion of the spleen and kidneys. In some instances there may be very little of significance

TABLE I: REACTIONS FOLLOWING PENICILLIN THERAPY

Reaction	*Bibliography*
Peripheral neuritis	JAMA 132:323 (Oct. 12) 1946.
Dermographia	Arch. Derm. & Syph. 54:66 (July) 1946.
Delirium	Brit. M.J. 1:240 (Feb. 5) 1949.
Mycocarditis, arteritis, and focal hepatic, splenic, and renal granulomata	Am. J. Path. 28:437 (May-June) 1952.
Purpura	Ann. Int. Med. 34:1219 (May) 1951.
Swollen tongue	Cincinnati J. Med. 28:321 (May) 1947.
Myocarditis	JAMA 143:361 (May 27) 1950.
Arthritis	Ibid.
Hepatitis	Ibid.
Loeffler's syndrome	Ann. Int. Med. 38:113 (Jan.) 1953.
Bronchial spasm	J. Mt. Sinai Hosp. 14:460 (Sept.-Oct.) 1947.
Ocular dermatitis	Arch. Ophth. 35:145 (Feb.) 1946.
Oral hemorrhage	Brit. M.J. 2:760 (Nov. 16) 1946.
Agranulocytosis	Ann. Int. Med. 25:732 (Oct.) 1946.
Asthma	JAMA 128:183 (May 19) 1945.
Eosinophilia-asymptomatic	Ann. Allergy 6:675 (Nov.-Dec.) 1948.
Hypoprothrombinemia	JAMA 140:1127 (July 30) 1949.
Cheilosis	Brit. M.J. 2:638 (Oct. 26) 1946.
Local hemorrhagic-necrotic skin reaction	J. Pediat. 38:630 (May) 1951.
Intestinal ulceration and hemorrhage with associated dermatologic reactions and vascular necrosis	New Eng. J. Med. 242:814 (May 25) 1950.
Anaphylactic purpura	M. J. Australia 34:305 (March 8) 1947.
Sterile abscess formation	JAMA 134:1475 (Aug. 23) 1947.

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On dosage of 1 Gm. per day for 120 days, ototoxicity was as follows*:

	Vestibular damage, % of patients		
	Mild	*Moderate*	*Total*
Streptomycin	12	6	18
Dihydrostreptomycin	6	0	6
Distrycin	0	0	0

	Cochlear damage, % of patients		
	Mild	*Moderate*	*Total*
Streptomycin	0	0	0
Dihydrostreptomycin	12	3	15
Distrycin	0	0	0

Heck, W.E.; Lynch, W.J., and Graves, H.L.: Acta oto-laryng. 43:416, 1953.

Distrycin dosage is the same as for streptomycin. In tuberculosis the routine dose is 1 Gm. twice weekly, in conjunction with daily para-aminosalicylic acid or Nydrazid (isoniazid). In the more serious forms of tuberculosis, Distrycin may be given daily, at least until the infection has been brought under control.

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found at autopsy. Several observers have stated that post-mortem findings are often the "guinea pig anaphylactic lungs."

LESS COMMON REACTIONS

Many case reports of hypersensitivity to penicillin appear in the current literature which do not correspond to the previously considered common types. Although reactions in large variety have followed penicillin administration, some may, of course, not be due to penicillin.

Table I illustrates many of the unusual reactions following penicillin reactions. There is no intention to draw conclusions or discuss the findings but merely to point out the extreme variability of "penicillin reactions."

Undoubtedly many more unusual reactions following penicillin therapy have and will occur. Many such manifestations are probably not caused by penicillin, although some of the listed reactions appear to be well proven cases of penicillin hypersensitivities.

Prophylaxis of hypersensitivity reactions: Seigal[39] is of the opinion that with repeated exposure to penicillin through the years, largely by injection, increasing numbers of persons are becoming sensitized to the anaphylactic level.

"The era of mild acceptable nondisabling post-penicillin reactions is changing to include graver complications; guilt is in usage; penicillin is not a cure-all."[40]

Certain precautions are worthy of serious considerations before instituting treatment with penicillin:

1. Avoid the use of penicillin for trivial or doubtful indications.

2. Secure a careful history of previous penicillin treatment and all adverse effects. Previous reactions of any type are significant. Accelerated and especially immediate reactions are of extreme significance. If previous reactions are recognized, the best therapy is to use a different antibiotic having the same bacterial spectrum.

3. Oral penicillin is apparently less likely to cause the severe immediate constitutional reactions than is the parenteral route. Topical application is well known to be a frequent sensitizer and is best avoided.

4. The possibilities of activating an old fungus infection is real.

5. Patients having conditions which apparently will respond to penicillin only, and who are suspected of being hypersensitive to the drug, should have preliminary skin tests. An additional helpful precaution might well be the oral administration of a 50,000 unit penicillin tablet ten minutes before the intramuscular injection.

6. Waldbott[41] suggests that it may be wise to inject the first drop or two, then pause for forty-five seconds before completing the injection, as the really violent reactions may become evident within seconds.

7. An additional precaution is modification of the technique of injection; the initial or potentially shocking dose being given into the arm rather than into the buttock so that a tourniquet may be applied if necessary.

Of these precautions, the first is of prime importance. The use of "prophylactic penicillin" is of questionable usefulness except, perhaps, for those conditions for which it has been of well established value as in rheumatic fever. Penicillin is a specific drug, its use is to be sanctioned only when it is administered for specific chemotherapeusis.

Treatment of the hypersensitivity reactions: The treatment of these hypersensitivity reactions is symptomatic. Prompt institution of treatment as soon as a diagnosis is made will often result in remission. The antihistaminic drugs are of value in relieving the pruritis and severity of the urticarial lesions. Bed rest is valuable and sedation is often indicated in the apprehensive patient. The more severe forms of serum-sickness, severe dermatological reactions, and anaphylactoid reactions are often afforded relief by ACTH or cortisone. In the immediate anaphylactoid type of reaction, of course, the treatment is that of any anaphylactic reaction with epinephrine the main reliance.

Reports in the literature often point out that mild reactions may not interfere with the continuance of penicillin therapy. It seems to me that continuing penicillin therapy in the face of an allergic reaction, be it even the mildest reaction, is inviting trouble. With the development of newer antibiotics it appears reasonable to substitute another antibiotic for penicillin even though it may be somewhat less efficient rather than to take the chance of superimposing a disease more severe than that for which therapy was instituted.

EFFECTS RELATED TO BACTERIAL ALTERATION

It has been shown that adverse effects of penicillin therapy may be produced by changes in the host; adverse effects may also be produced by changes in the bacteria, altering the bacteria in such a manner that penicillin no longer can be used as a therapeutic tool.

Bacterial resistance: The mechanism of evolution in the biological kingdom is considered to be spontaneous mutation followed by natural selection or "survival of the fittest."

This problem of bacterial resistance to penicillin in clinical medicine has been largely concerning the staphylococci and the enterococcal streptococci. There has been no evidence of decreased activity *in vivo* of the more sensitive bacteria: gonococci, pneumococci, or beta hemolytic streptococci. Penicillin treatment of syphilis has not been affected by drug fastness.

As stated, staphylococci comprise the largest and

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most important single group of resistant bacteria. It appears to be generally agreed that there are two kinds of resistance to penicillin in staphylococci: (1) One is that which can be induced artifically *in vitro* and was first described by Abraham et al.[42] in 1941. This type of resistance appears to be temporary in duration and exhibits morphological and Gram-staining changes and is accompanyed by a loss in virulence. (2) The other type of resistance is that which is known as "natural resistance," produced by virtue of the ability of the micro-organism to change its metabolism or to produce penicillinase and to retain full virulence for experimental animals.[43] The subject has been a widely controversial one. The production of penicillinase is one physiological mechanism of the bacteria to develope resistance, the one which has received the widest publicity. However, several other mechanisms may also be responsible for this resistance.[44]

Do staphylococci readily become resistant to penicillin *in vivo,* and if so, in what way does this resistance differ from the kind acquired *in vitro?* Barber's suggestion[45] is that what appears to be an increase in penicillin resistant staphylococci following or during therapy may really be the result of a selective process in which sensitive bacteria are destroyed, while resistant ones survive and proceed to multiply.

In a report of three cases of fatal staphylococcus enteritis occurring after prophylactic penicillin and dihydrostreptomycin, Fairlie and Kendall[46] point out that the concept that this complication is due to suppression of normal intestinal flora permitting pathogenic overgrowth of intestinal staphylococci appears to be oversimplified. A direct stimulation of the staphylococcus by antibiotics must be considered. This interesting idea needs more observation and study before it can be fully appreciated.

Attention to the prevalence of penicillin resistant staphylococci brings a recognition of a gradual elimination of sensitive strains. The increased resistance of these pathogens has been noted especially in hospitals or areas where penicillin is widely used. Rountree, et al.[47] reports that the number of resistant strains isolated from outpatients is roughly one-half that from in-patients. The present information does not indicate that naturally occurring staphylococci carried by the population at large are frequently resistant to penicillin. Barber,[48] studying the same population group in the same hospital in 1946, 1947, and 1949, reports the incidence of penicillin resistant strains to be 14 per cent, 38 per cent, and 59 per cent in successive years. Howe[49] in 1953 found that 50 to 75 per cent of staphylococci were resistant to penicillin.

The second area in which clinical medicine must deal with bacterial resistance is the group of enterococcal streptococci. Finland[16] points out that some decrease in the efficacy of penicillin is responsible for the present need for large dosages in the treatment of subacute bacterial endocarditis. He states that the widespread use of the antibiotic has resulted in general (not marked) reduction in the sensitivity of strains of the viridans group of streptococci. Dowling[50] reports that in 1951 about one per cent of the cases of subacute bacterial endocarditis have infecting organisms which are highly resistant to penicillin.

Penicillin resistant strains of pneumococci,[51] beta hemolytic streptococci,[52] and gonococci[53] have been produced in the experimental laboratory *in vitro.* This offers interesting speculative material for the future chemotherapy of diseases caused by these micro-organisms.

Cross resistance to antibiotics: Antibiotics with presumably similar mechanisms of action may cause the emergence of forms resistant to each other. This work needs to be explored at greater length for more conclusive information. The present concept of antibiotic cross resistance is given in table I.

TABLE II: ANTIBIOTICS WHICH EXHIBIT CROSS RESISTANCE[50]

Group I	Streptomycin Dihydrostreptomycin Neomycin Streptothricin
Group II	Chloramphenicol Chlorotetracycline Oxytetracycline Tetracycline Penicillin (probably)
Group III	Erythromycin Carbomycin

It should be pointed out that only by promptly terminating infections can the emergence of resistant strains be prevented. This, of course, implies recognition of the etiologic agent and prompt institution of treatment with the drug of greatest efficacy in adequate dosage.

Bacterial resistance has important epidemiological aspects. The widespread use of penicillin among the hosts has led by a selective process to a widespread distribution of staphylococcic strains resistant to penicillin. Since many, though not all, resistant strains of bacteria appear to be as virulent as their sensitive parents, they persist in the population.

Antibiotic combinations: Is is not within the confines of this paper to discuss the problem of combined antibiotic therapy. However, because of its importance and relevance, this large and interesting subject should be mentioned. Indeed, adverse effects of penicillin therapy may be brought about, whether it be through the production of resistant bacteria, failure of treatment, or masking a diagnosis, by combinations of other antibiotics with penicillin.

Jawetz[54] has been engaged in experiments on this

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subject, the results of which have aroused a great deal of interest. Table III is a brief consideration of his results.

TABLE III: ACTION OF ANTIBIOTICS IN COMBINATION

Group I	Penicillin, streptomycin, bacitracin, neomycin (probably polymixin)
Group II	Chloramphenicol, chlorotetracycline, oxytetracycline, erythromycin, carbomycin (sulfonamides behave like group II)

Members of group I are frequently synergistic, occasionally indifferent but never antagonistic to each other.

Members of group II are neither synergistic nor antagonistic with each other but simple additive effects are often observed.

The addition of group I to group II may result in synergism or antagonism, depending in part on the sensitivity of the bacteria to the group I drug.

The material available at the present time has been aptly summarized by the Cornell Conference on Therapy.[55] "There is, as yet, insufficient experience with these matters in human infections to define the meaning of these interesting experiments in relation to therapy. The situation in actual treatment is sufficiently different and unpredictable to make it impossible to put the matter of combined therapy on a sound base, but enough is indicated by these experimental observations to suggest the possibility of doing good as well as harm in the treatment of infections."

Superinfections: This group of adverse effects of penicillin therapy in many aspects is similar to those resulting from penicillin resistance; however, they are sufficiently different to merit separate consideration. The spontaneous occurrence of new infections during the course of treatment with penicillin is a complex and not uncommon problem.

Changes in the bacterial flora of the body during penicillin therapy have been studied by many workers since the drug first became available. As one would expect, the bacteria sensitive to the drug are suppressed by treatment.[56, 57] Weinstein[58] offers two explanations for spontaneous occurrence of new infections during treatment: (1) A suppression of certain groups of bacteria with an increase in other groups usually results in no untoward effects; however, in other cases, such alterations in flora result in a rapid growth of virulent bacteria originally present and not susceptible to the antibiotic. If general resistance to infection in the host be depressed, new infection results, invasion occurs, and new disease develops. (2) Spontaneous occurrence of new infection may also occur as a result of contamination in the administration of penicillin.

Sommer and Favour[59] stress the importance of previous chronic pulmonary disease, of general debility and of the presence of a mixed gram-positive and gram-negative flora in culture of the respiratory tract before treatment in the pathogenesis of infectious complications.

Hypersensitivity studies correlating previous fungus infections and penicillin reactions has been stated. Schnurman[60] described latent tricophyton infections activated by the use of penicillin in which there was actual recurrence of apparently cured infection. Sanchey-Cuenca[61] proposes an interesting possibility in which penicillia may be pathogenic. Penicillia are frequently recovered from the feces in routine stool examinations, being present in the intestine as a saprophyte. The mold may be present in pathogenic form in lung abscesses. Is this a superinfection? It is possible that the presence of penicillia in the host may predispose to sensitization to penicillin. More study is needed before this condition, termed penicilliosis, can be fully understood.

Overgrowth by monilia has been frequently seen with antibiotic therapy. It is less often encountered when penicillin is used alone than when used in combinations, especially with the broad spectrum antibiotics. It is often noted following the local use of penicillin troches or lozenges. Multiple vitamin B preparations have helped clear up these monilial overgrowths.

Signs or symptoms arising during treatment with antibiotics that are not explainable by the existing disease process should be carefully studied. The simple gram-stained smear of pathological material may permit an immediate diagnosis and prompt institution of proper drug therapy. Cultures and sensitivity studies should be done *in vitro* for further advantages in future management.

EFFECTS RELATED TO PENICILLIN AS A PRIMARY TOXIC AGENT

For practical purposes the possibilities of penicillin as a direct toxic agent are negligible except following its intrathecal use. The large number of individuals receiving the drug in massive dosages for the treatment of bacterial endocarditis and syphilis attest to the drug's low toxicity.

The effects of penicillin on the central nervous system are those of stimulation, twitching, and convulsions. The convulsive factor appears to be related to the antibiotic properties of penicillin because seizures diminish directly proportional to the destruction of the antibiotic properties by aging, boiling and acidifying and by dissolving penicillin in alcohol.[62]

Intrathecal reactions include headache, vomiting, vascular collapse, cyanosis, convulsions, unconsciousness, flaccid paralysis of the extremities, with increased spinal fluid cell count and protein values.[63]

Toxic psychosis occurring following intramuscular injection with oral administration is reported but was felt to be due to edematous lesions of the brain resulting from a localized penicillin sensitivity.[62]

From our present knowledge, these effects on the central nervous system are apparently due to irritative

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phenomena rather than hypersensitivity. Weinstein, et al.,[64] following a study of intrathecal chemotherapy in bacterial meningitis, have concluded that intrathecal administration of penicillin is attended by a negligible risk of producing nervous system damage provided the dose and dilution of the drug is meticulously adjusted. They state that doses in excess of 30,000 units should not be given into the subarachnoid space of adults and the quantity must be reduced proportionately for children.

EFFECTS ON PATIENT CARE

Adverse effects of penicillin therapy in regard to patient care are numerous. First, it should be recognized that all of the aforementioned adverse effects add greatly to the patient's morbidity. Indeed a more serious illness may be the result of the therapy than the original problem for which the patient sought medical care.

A delay in diagnosis occurs probably more often than is realized. The mechanism by which this happens is considered to be a condition in which enough of the drug is given to mask signs or symptoms without producing a cure. It is often found that bacterial identification cannot be accomplished after penicillin is given. The importance of this fact is obvious when one considers the fact that valuable time may be lost before definitive therapy can be instituted.

Little material is to be found in the literature on this particular subject. Therefore, the diseases listed below are taken from my own experience. The list is not considered complete by any means, but should serve as illustrative material.

Diseases in which a delay in diagnosis resulted from indiscriminate use of penicillin: (1) diphtheria, (2) poliomyelitis, (3) Friedlander's pneumonia, (4) tuberculosis, (5) meningitis, and (6) carcinoma of the lung.

Some illnesses require prolonged treatment. A definitive diagnosis rests upon identification of the bacterial cause. This can usually be done only before antibiotics are given. The most common of these diseases are subacute bacterial endocarditis, osteomyelitis, tuberculosis, and brucellosis.

SUMMARY AND CONCLUSION

The adverse effects of penicillin therapy have been classified and discussed as (1) hypersensitivity reactions, (2) effects related to bacterial alterations, (3) direct toxic reactions, and (4) effects on patient care.

In so far as possible, each of the adverse effects commonly encountered has been considered as to incidence, characteristic features, diagnostic aspects, prophylaxis, and treatment.

Although the clinical evaluation of penicillin is still far from complete, it is the intent to give some perspective of the untoward aspects of treatment with this drug.

Penicillin remains a valuable, indispensable drug. It is, however, very probable that with repeated exposure to penicillin through the years, an increasing number of therapeutic difficulties may be encountered.

Penicillin is a specific chemotherapeutic agent having specific indications for its use. The indiscriminant use of this antibiotic is condemned.

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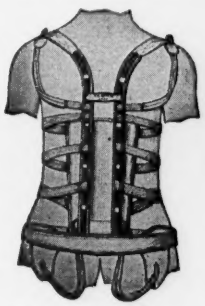

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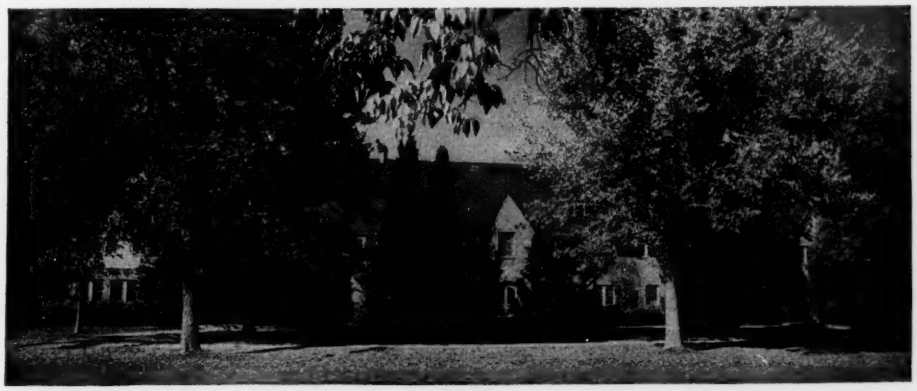

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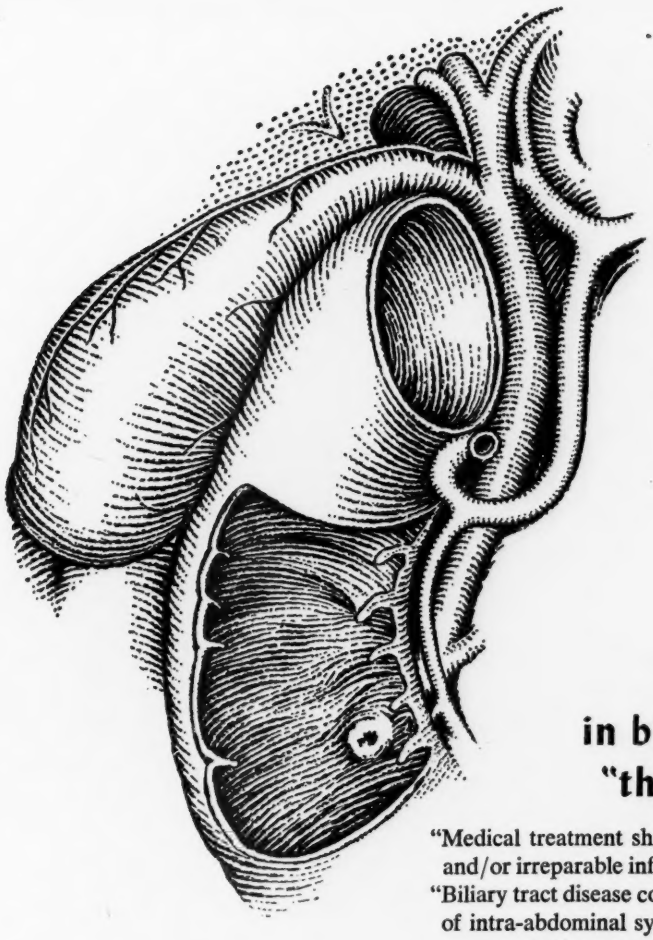

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